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"The Modern Treatment of Diphtheria"

by

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INTRODUCTION.

It is proposed in the following Thesis to record a few clinical observations and impressions, gained from a study of nearly 1,600 cases of Diphtheria, which have been under my care at the City Hospital East, Old Swan, Liverpool, during the past four and a half years, and to discuss an analysis of these, at the same time dealing with the whole subject of the treatment of diphtheria, comparing the results in the pre-antitoxin period with those of the antitoxin period.

Subjects of a highly technical or abstrusely scientific nature have not been approached, these being relegated to laboratory investigators and others with better opportunities than I possess. My object is simply to record the points observable at the bedside of a patient and to express my personal ideas thereon.

Although serum therapy is now a well established fact, it is nevertheless useful to publish results in a large series of cases, as information may be gained on various details such as Dosage, Effects of early and late administration, Sequelae, etc.

As a preamble to the discussion of the methods of to-day, in reference to Diphtheria, a short resumé of the History of the malady has been given. Commencing with the days of earliest times, we have evidence from the writings of the Old Masters of Medicine, of the

existence of the disease. With the passage of years, observers became more numerous and descriptions more faithful in their portrayal. Theories too were propounded, some indeed, accidentally without doubt, very nearly approaching our present ideas. The first milestone, however, which marked the route towards a final solution of this and innumerable other scientific problems was essentially the discovery of the microscope by Leuwenhoek in the 17th century.

The way thus paved towards the study of minute vegetable and animal bodies finally led to the science of Bacteriology. From the study of Bacteria it was but a comparatively short step to observe, and analyse where possible, the substances produced by these micro-organisms, and the effects thereof.

The establishment of the Klebs-Loeffler Bacillus, so named after its discoverers, as the causative entity, (83-4) the isolation of its toxin by Roux and Yersin (88-9) and the ultimate elaboration by Behring (92) of a specific antitoxin, are the outstanding incidents in the sequence of events which have terminated in the placing of Diphtheria and its Cause and Treatment, upon a scientific foundation of comprehension, the like of which is not known for any other disease.

The modern treatment of Diphtheria may be said to date from Behring's discovery of the antitoxin. A method of standardising the serum was enunciated by

Ehrlich and Behring, and in 1893 the making of serum on a commercial scale was commenced and the article was placed upon the market. By the following year its employment had been instituted generally over Europe and America and the pre-antitoxin days had ceased to exist.

It is interesting to observe the change in the mortality rates in the years preceding and succeeding the institution of Antitoxin treatment; and the following data, taken from the Metropolitan Asylums Board Annual Report, 1908, are chosen as being most representative:

<u>Years.</u>	<u>Mortality per cent for all forms.</u>	<u>Tracheotomy Cases.</u>
1890-1893. No antitoxin in use.		
Average.	30.4	66.2
1894 Antitoxin only occasionally used.	29.6	70.5
1895 Antitoxin regularly used.	28.1	50.2
1896	25.9	40.6
1897	20.4	39.9
1898	17.3	37.
1899	15.4	39.1
1900	12.9	33.6
1901	12.6	30.2
1902	11.8	31.9
1903	10.2	29.7
1904	10.9	31.3
1905	9.	27.6
1906	10.4	36.6
1907	10.4	29.
1908	10.9	27.8.

Such figures as these speak for themselves. But fairness compels one to the admission that the change may not entirely be due to Antitoxin. Better means of

diagnosis and hence greater exactness in ultimate classification must have had some effect upon clinical data, particularly in regard to Diphtheria, in which the bacteriological diagnosis is moderately complete. Consequently many cases, which previously had not been recognised as true Diphtheria, are now diagnosed correctly. It is, however, in referring to the laryngeal forms and especially those requiring tracheotomy that the benefits are made even more manifest, for in these cases the bacteriological factor is almost eliminated, as many of them do not give a positive culture from a swab from the throat, and again in many cases the necessity for operation is of such urgency that the result of a bacteriological examination cannot be waited for.

HISTORY.

Of the various diseases of the infectious group which have prevailed from time to time in epidemic form, Diphtheria is believed to be one of the oldest.

In none of the writings, however, of the Ancient Greek physicians, of Hippocrates and his pupils, is one able to locate any reference to the disease. Neither Celsus, Soranus, Galen, nor Caelius Aeronius ever make mention of a like condition either as a sporadic or an epidemic malady.

On the other hand, the disease appears to have been well known in Egypt, Syria and Palestine, even in ancient times, as is proved by repeated references to it in the Babylonian Talmud, a work which, though it only appeared in the 5th century transmitted all the old Jewish traditions (Wünsche¹, Strack²).

In the Berachoth Treatise the following occurs: "There were created 903 kinds of death in the world.... the hardest of all Angina (according to Strack "Askara") the easiest of all Kuss."

"Angina is like a briar in a bundle of wool which one casts behind one (for it is as difficult for the soul to leave the body as to remove a briar from a bundle of sheeps' wool)." According to some "it is like a ship's cable in the opening of the throat (for a ship's cable can only be drawn with difficulty through

a small hole)". The Kuss is "like unto a hair which one draws out of the milk". "Askara", it has been suggested by Strack, is connected with the word "šāk-har", to stop up, i.e. designating a death from choking, and therefore should now be translated as Diphtheria.

The first accurate description of Diphtheria recorded is that of Araet^{us} (Mann³) the Cappadocian physician, who lived in Rome in the latter part of the first century. This observer gives a faithful picture of the disease, describing the varieties of angina, benign and malignant, and noting the possibility of its extension to the respiratory tract, and the occurrence of death by suffocation, of which he gives a remarkably perfect description, drawing attention even to the characteristic foetor. He mentioned the frequency of the malady amongst children and the prevalence in certain countries, Egypt and Syria particularly, whence the names "Syriac and Egyptian ulcer". It is remarkable that he describes no epidemics, a fact which leads to the inference that the disease must have occurred only sporadically and never attained epidemic dimensions.

During the 4th century a similar disease became epidemic in Rome and was described by Macrobius.

The next and more characteristic description of

note is that of Aetius⁴ (1542) of Amida in Mesopotania, who lived in the court of Justinian at Byzantium.

Amongst other factors he makes reference to palatal paralysis as one of the sequelae of Diphtheria. The treatment he suggests is interesting, comprising amongst other remedies various astringent plant juices mixed with honey, and more especially the dung of dogs which had previously been fed upon bones, or the excreta of boys who, two days before had been fed upon bread and lupins, or, in desperate cases, dusting with dried and powdered crocodile bile or anointing with honey.⁵

The earliest mention of epidemics in the European countries, is that of a pestilence "Esquinancia"⁶ (corresponding to "Squinantia" the name subsequently given to Angina Maligna) which raged in the year 580. The same writer (Hirsch) states that Baronius spoke of similar throat pestilences which occurred in Rome first in 856 and again in 1004. In 1039 an almost parallel visitation took place in Byzantium; the name given in this instance to the disease was "Cynanche". Short (1799) it is said, mentioned a kind of Angina which broke out in England in 1389 and carried off a large number of children. In 1517 the Rhine country was visited by an epidemic of a disease with "white fungus" in the throat.

It was about the year 1581 that a vast pestilence

marched over Spain. The disease "Garotillo" or Morbus Suffocans was undoubtedly true Diphtheria, and raged in Spain and later in Italy for nearly sixty years. Many are the descriptions of contemporary writers and numerous are the clinical points they observed; the white deposits on the pharyngeal surfaces later becoming darker, the laryngeal and occasional nasal involvement, the horrible foetor due to gangrene, the suffocative death, are all mentioned. The infectious nature of the disease was suggested by Cortesius who also gave the name "Gulae Morbus" to the condition. In 1642 the disease died out. But after a period of quiescence of about seventy years the pestilence again flared up. From Italy and Spain it traversed to France (1730) and thence to Holland. Other contemporary observers include De Fontecha¹⁰ (1611), Villa Real⁹ (1611), Herrera⁸ (1615) in Spain, and Alaymus (1632) and Cortesius⁶ (1625) in Italy.

Eventually it reached England and was described minutely by Fothergill, Starr, Huxham, and others. Switzerland, Germany, and Sweden also were visited at this period, and simultaneously it was carried to America. In 1771-2 it was epidemic in New York. Samuel Bard⁷ at this time published a brochure entitled "An Enquiry into the Nature, Cause, and Cure of the Angina Suffocativa or Sore Throat Distemper, as it is commonly called by the inhabitants of this City and

Colony". In it he speaks in such a manner as to substantiate the inference of his belief in the Angina and the croup being merely varieties of the same group. He appears however, to have included in his descriptions, other of the anginose diseases particularly Scarlet Fever and Measles; for he makes mention of inflamed, watery eyes, a livid and bloated countenance, with a few red eruptions here and there upon the face. Douglass, a contemporary of Bard, appears also to have fallen into the last named error.

Caldwell (1816) states that Washington himself contracted the disease at his country seat, Mount Vernon near Alexandria.

During the pandemic of the 18th century, the formation of tubercular membrane in the larynx and trachea was first described by Ballonius¹¹ (1762). Speaking of the death of three children, in his second treatise on epidemics and ephemerides he describes a disease "affectio orthopnoica" from the dyspnoea causing death; due he thought to neither a "catarrhus suffocans" nor a failure of the lungs, but possibly to an affection kindred to the "pulmo repletus" of Hippocrates. One thing is certain from his description - he regarded the condition from which the children died as a new one.

Ghisi¹² (1749) was the first to link the tracheal type with the pharyngeal under the name of "Angina

strepitosa perfida mortalis"; he noted the occurrence of the nasal voice and regurgitation as sequelae to the tracheal form.

Tub~~er~~ular membrane was also described in France by de Nobleville¹³ (174) at Orleans, and Malouin¹⁴ (1746-7) in Paris. By Starr¹⁵ (1752) in England as products of a disease which he termed "morbus strangulatorius". An epidemic in Frankfort in 1758 was written upon by van Bergen;¹⁶ he called the disease "morbus truculentus infantum" and described the false membranes thus:- Tussi rejecit tubulum membranaceum, qui portio membranae tubulosae per ramos bronchiorum durante morbo generata fuit.

In 1765, Francis Home¹⁷ a physician of Edinburgh, published a book "An enquiry into the nature, cause and cure of croup" which he described from 12 cases, as a new disease, known locally on the West Coast as "Chock" or "Stuffing". It was pictured by Home most graphically, and by reason of the symptomatic shrill voice and difficult breathing was termed "Suffocatio Stridula" by him. He noted that it was especially common in children, particularly the very young, and stated that he had neither seen nor heard of a case over 12 years of age. Damp weather, the cold winter months, and propinquity to the sea were, he found, predisposing factors. Two forms were described by him, a simple

catarrhal form (benign) and a malignant form showing the occurrence of false membrane in the upper part of the trachea and spreading downwards. The membrane was easily detached from the underlying tissues, if not entirely unattached on account of there being "pus behind it". He particularly mentions the rarity of the new disease, in Edinburgh at least, and states that some may go through a whole life and not see a single case, or, at most only one or two. His treatment consisted in venesection, leeches, blisters to the neck, attention to the bowels, and the inhalation of steam and alcohol vapour. Sudorifics or emetics he found to be of no special utility. The membrane once having formed, he recommended that its removal be attempted, or, if necessary, that tracheotomy be performed. This treatise, which aroused the attention of the whole medical world, actively stimulated the study of the disease, and Home's observations were confirmed everywhere by numerous writers; some, like Home only met with odd cases here and there, i.e. sporadic, whilst others described epidemics, the latter writers including Lep-ecq de la Clôture¹⁸ (1778) in the Lower Seine Department and Ramsey¹⁹ (1786 circ.) at Chesham. Cases of the type described by Home were described as occurring together with those of the "angina gangrenosa maligna" type.

Samuel Bard²⁰ (1789) and Johnstone²¹ (1779) and others hence regarded them all as being of the same nature, and related to one another.

The difficulty however, of actually differentiating these diseases was very great. In fact it was not until the discovery of the causal agent of Diphtheria was made, that any satisfactory classification could be accomplished. The matter was rendered even more difficult when John Millar in 1769 described under the name of "Asthma acutum" a disease clinically resembling croup in many ways, save in the lack of cough, the rattling rather than whistling respiration and the absence of membrane.

Acting upon the impetus given by Home's treatise, the Société Royale de Médecine de Paris in 1785 offered a prize on the subject "Si la maladie connue en Ecosse et en Suede sous le nom de croup ou angine membraneuse existe en France?" Numerous were the papers sent in, and the successful one was that of Vieusseux²² (1812) who demonstrated its existence in Geneva and probably in France. The other papers showed its existence in France as general. From the point of clinical value however, they added little to knowledge, beyond the fact of diminishing frequency of croup. Interest in the subject of croup was a few years later again stimulated when a nephew of Napoleon I. a son of Louis Napoleon, King of Holland, succumbed to an at-

tack. In June, 1807, Napoleon offered another prize for a thesis upon the subject.

Royer Collard²⁴ (1813) adjudicated and awarded the prizes to Albers²⁵ (1816) and Jurine²⁶ (1816). The essay of the latter was of special interest: "Gangrenous angina, Cynanche maligna, or angina gangrenosa is a disease which in a pharyngeal, laryngeal or tracheal form. In the latter form it might easily be confused with croup, one of whose symptoms namely the false membrane, it exhibits, if it did not at the same time possess other distinguishing characteristics."

He then speaks of the difference between gangrenous angina and "the epidemic gangrenous angina of children", this latter assuming croup sometimes like characters, which he states are the result of the "putrid influence of the epidemic". From the study of the writers and taking into account "the predisposition of children to it, the rapidity with which membrane forms and the condition of the spots or ulcers upon the tonsils and pharyngeal region, we are tempted to doubt the existence of gangrene as a specific disease, in the majority of these cases, and to regard the disease as modified croup which has merely assumed another form owing to the putrid influence of the epidemic, and to term it aphthous, putrid or malignant croup." He denies the infectious nature of croup; and states that people came to that idea because it occurred in

association with epidemics of gangrenous angina, German Measles, smallpox, chickenpox, and scarlet fever, Croup is simply in his idea, an adventitious phenomenon and was due to the "checking of the perspiration by the access of cold air".

These essays, however, were directed mainly towards arriving at a routine of suitable treatment and dealt with the question of croup as an inflammatory or non-inflammatory condition; some held to it being the former and others to the latter, and among the latter partisans Lobstein²⁷ (1817) was notorious. He held that croup was not a specific haematogenous condition but a catarrh plus a nervous element. The false membrane was not the crucial factor since the patient often dies despite the removal of the obstructing membrane and the consequent freeing of the respiration. Ten years before, Astenrieth²⁸ (1807) had expressed similar ideas. He deemed the condition due to a "concentration of irritability towards the air passages". Besides application of mercury, he first applied clysters of vinegar in order to drain the morbid material towards the stomach, and later, cutaneous irritants to impel it towards the surface of the body and so divert the concentration of irritability. The pathological products in the throat did not count for much in his view; in fact, because it increased the irritability of the parts, he was inclined to discountenance local treat-

ment. The advisability of tracheotomy he denied. His expressed ideas point to his recognition of the condition as a distinct disease due to a definite pathological substance in the blood, and conferring immunity after recovery. His superstitions as to Constellations, etc., however, so hampered him as to make him unable to declare it infectious. Membraneous angina and "millar's asthma acutum" were identical he states, but he makes no mention of their relation to angina maglina.

During the eight years succeeding 1818, epidemics resembling the "Garotillo" in Spain occurred in Tours, La Ferrière and Chenusson, and it was with the material thus supplied that Bretonneau²⁹ (1826) based his observation which he published in his monumental "Traité de la diphtherite, des inflammations specials du **tissues** muqueux et en particulier de la diphthérie ou inflammation pelliculaire connu sous le nom de croup, d'angine maligne, d'angine gangreneuse etc."

"In the year 1818 the garrison of Bourbon Vendee was transferred to Tours and many fell ill there of a disease characterised by ulcers in the mouth, inflammation of the gums, and breaking of the teeth followed by grey green deposits upon the mucous membrane of the lips and cheeks. From the mouth of the sick persons there emanated a most pestilential odour and the neighbouring lymphatic glands began to swell. The disease

was first regarded as Scorbutic gangrene of the mouth, and Bretonneau, soon recognised that it could have no connection with Scurvy because the persons attacked were otherwise healthy, and also because it assumed all the features of angina maligna, when it attacked the tonsils and throat. Bretonneau attributed the striking fact that it primarily attacked the gums to the use of drinking vessels in common. When the garrison was replaced after a time by another section of troops, the disease appeared among the latter in the form of severe angina maligna. Within a few months of the introduction of the disease by the soldiers of La Vendée to Tours, 60 persons of all ages, mostly however, children, died from it. Some fell ill of severe gangrenous angina, others of typical croup.

An accurate clinical and pathologico-anatomical investigation of all these cases led Bretonneau to the conviction that all of them were caused by one and the same disease, to which he gave the name "diphthérie" (διφθερία; the skin) in order clearly to distinguish it.

The production of membrane by the actual virus was to him the characteristic mark of the disease, because in the severe, apparently gangrenous forms he found at the autopsy not the expected gangrene of the mucous surfaces, but a membrane of a greyish green colour, owing to a decomposition of the blood mixed

with it, lying upon the slightly altered tissues. This was the source of the pestilential odour which had suggested a gangrenous condition. The association of malignant angina with typical croup, which he had observed in many cases, at first led him to think the condition might be due to the occurrence of two diseases simultaneously, but the observation that adults who were suffering from malignant angina could infect children with typical croup, and the fact that the deposit on the tonsil and pharynx exhibited the same structure as the membranes of croup convinced him that croup and malignant angina must be dependent upon the same disease-producing factor. He further states very decidedly that scarlatinal angina has nothing in common with Diphtheritic angina, because the Diphtheria membrane is formed upon the mucous membrane and can be detached, whereas in scarlet fever the change is in the mucous membrane itself and the deposit cannot be removed. The keen-sighted observations and deductions of Bretonneau, led to the conclusion that Diphtheritis although occurring under different forms is a single etiological ens morbi, just like Scarlet Fever, Measles and Smallpox." (Loeffler: History of Diphtheria.)

Trousseau³⁰ (1828) confirmed and extended Bretonneau's fundamental investigations, but differed with certain of his deductions and in order to indicate his non acquiescence with Bretonneau's idea that the

condition was a purely local one, he substituted the name "diphthérie" for "diphtherite", because he considered the specific changes upon the mucous membrane to be essentially the local product or manifestation of a general condition or disease. Bretonneau himself subsequently accepted this new name. He also spoke of it as "Egyption diphtheria", to commemorate the land of its origin.

A digression is here made to refer briefly to the Epidemiology of Diphtheria during the 19th century.

During the 19th century the disease spread its tentacles to many parts of the globe. Now quiescent for a period, it would suddenly break out again with added strength. The twenties saw isolated epidemics in Europe. With the forties occurred a comparatively mild visitation involving Europe and America. A period of calm followed for a few years but the middle of the fifties was marked by a conflagration involving practically the entire world. Commencing in France it marched radially, almost decimating the child population of some districts particularly in Bessarabia. Iceland in 56 encountered the disease for the first time. In two decades or so, hardly a corner of the world remained untouched. In 1866 an epidemic commenced in Pekin which carried off thousands of the population. The year 1877 saw Japan attacked for the first time

and the disease has remained endemic there since, The sudden recrudescences of Diphtheria in regions from which it has temporarily disappeared, may not entirely be independent of the increased facilities for inter-communication and transit generally.

Trousseau regarded the disease as capable of killing not only mechanically but also by a systematic poisoning. He regards the membrane not as a primary lesion but as a result of infection.

By 1840 the personality of Virchow had begun to loom largely in matters relating to Pathological Anatomy. The writings of Bretonneau and his pupil Trousseau did not meet with the approval of the German pathologist, Virchow, (1844) enunciated his ideas of inflammation on mucous surfaces, classifying the processes as (1) Catarrhal, (2) Croupous and (3) Diphtheritic. Croupous inflammation he regarded as a superficial inflammation with production of small cells in variable number. Diphtheria he looked upon as a true interstitial process affecting the submucous layers, and properly described as gangrenous. He opposed the contention that croup and diphtheria were manifestations of disease the products of a common causative factor, and sought to establish the anatomo-pathological distinction. And so great was the personal power of the pathologist, that he soon won over many disciples to his cause. It

was not until bacteriology became the hand-maiden of the clinician that these divergent opinions were finally disposed of.

The next forty years were characterised by enormous activity, on the part of the clinician to some extent, but by the laboratory investigator to a far greater degree.

In 55, Bretonneau publicly deplored the differences between the Virchow School and his own and reasserted his convictions that all forms of the disease were contagious. He quoted the tragic occurrences in the Napoleon family. The illness of the Queen Hortense with a diphtheritic inflammation of the gums, the fatal seizure by laryngeal diphtheria of her eldest son, and the later contraction by the Empress Josephine, her mother, of diphtheritic angina from an extension of which she died of croup a few days later. He spoke of direct communication by way of softened mucous membrane, or abraded skin surfaces and quoted examples from contemporary incidents of a like nature and equally augmentative to his views.

The case of Professor Herpin (quoted by Jaffé) who contracted diphtheria of the nose by being coughed upon by a child to whom he was giving attention, his later development of paralysis and ultimate death.

Contemporaneously a case occurred at the Collège de la Flèche in which a child trod with naked feet upon

the expectoration of a diphtheritic patient and later developed the specific lesions between the toes. About 1865, a newer theory arose. It was to the effect that croup was set up by the inspiration of acrid irritant substances. Many investigators attempted this means, notably, Albers, Jurine and others, but were not successful. Bretonneau, however, produced it by injecting cantharides and olive oil into the trachea; and more striking results still, were obtained by Delafond who injected chlorine, corrosine sublimate, sulphuric acid, and ammonia, the last being particularly marked. Bretonneau, however, despite the similarity of cantharides croup in dogs and diphtheria in man, clearly recognised their difference by the marked dissimilarity in their course and unhesitatingly urged the specific differences.

The numerous animal experiments performed in this period cannot be recounted in this short resume. Suffice is to say that the success of the investigator and the failure of the efforts of that to obtain similar results were mainly the results of the darkness which still hung heavily over the aetiology of the malady; only with the advent of the light in the shape of bacteriology was this gloom penetrated and finally eliminated.

Principal among the investigators of the later period may be mentioned Billroth, Oertel, Lichtheim,

Huetu and Marceuse. The doctrine of the contagium animatum obtained an ascendancy about 1840 by attention being drawn to various fungi found upon the dead bodies of fish, silkworms, etc., and the beliefs that such fungi were the entities causative of death.

Laycock³² in Edinburgh in 1859, published his theory that diphtheria was caused by *Oidium Albicans*. Various observers supported, but others denied, and gave the *Leptothrix Buccalis* the aetiological distinction. The fungus or vegetable fons et origo of the disease was the stimulus for many experiments during this decade and the following, principally by Hallin, Oertal, and Nasiloff.

Eberth in 1872 in sections from tracheal^{ae} mucous membrane discovered spore like bodies in a tough ground work, with many young cells. The mucous epithelium which lay under this formation was usually present though cloudy and invaded by young cells. Micrococci also he found in the lymph channels, etc., near, but none in the kidneys, spleen, or other organs. Many other investigators supported these discoveries by the results of their experiments. In 1880 Letzerich³³ cultivated diphtheritic material upon solid medium for the first time, an isinglass medium in special glass containers being used, and which he called "Gallertkammern". The micrococcus *Diphtheriticus* he states were in "plasma cells" which he found in the walls of the

veins of the heart, and other tissues. Klebs, the year later did not find these plasma cells in the internal organs, but discovered them in large numbers in the membranes. He made cultures from material obtained by introducing fine capillary tubes into the tonsillar deposit of a child which had died from Diphtheria. Thus Klebs and Létzerich were the first to cultivate diphtheritic material upon solid media. To the organism thus found, and later on also found by his pupil Brown, and further studied by him, he gave the name *Microsporon diphtheriticum*. In 1883 at the Congress für innere Medicin at Weisbaden, Klebs recounted his later researches and described a second organism, a short slender rod, staining with methylene blue, and which he found in the more superficial layers of membrane. The rods contained spores at their ends. This statement was confirmed then by Edlefsen.³⁴ So far however, Koch's postulates were not all accounted for. In 1884 Loeffler published the results of his experiments which satisfied them. He found two groups of organisms, micrococci in post scarlatinal diphtheria and in the necrotic material and various bacteria in the surface layers of the thick false membrane with small rods arranged in groups more deeply. Cultivating them in peptone gelatine, and serum containing 25% peptone gelatine, differential examinations and inoculations were possible. Employing the cocci he used

mice, field mice, guinea-pigs, dogs and monkeys, and inoculated them in various ways. Certain died of septicaemia, the mice especially, but none with lesions suggesting diphtheria. From this he deduced that the cocci were merely adventitious or only secondary to the rods. Using solidified blood serum containing 25% peptone gelatine he grew the rods. Inoculation of guinea-pigs gave striking results. Rods, however, were only found in small numbers at the site of inoculation but none in the blood. Similarly rabbits showed like results. Owing to the small numbers of organisms found at the lesion and their absence from the blood and tissues he inferred that the disease was due to a poison elaborated locally but which got into the blood and was absorbed therefrom. Examining healthy throats, mouths and teeth, he found the rods in a few cases. This caused him much perturbation and hesitancy to regard the organism as the causal factor. (This etiological fact is with us today but is perhaps better understood.) In 1887 he published further work resulting in the finding of typical lesions post mortem in the stomach. Many observers including Babes, Sørensen, Roux and Yersin and others, followed the lead thus given. In 1890 Loeffler answered many objectors to his conclusions; an interesting fact mentioned by him was of two guinea-pigs which had survived inoculations but which later had manifested severe

paralytic lesions. He also stated that in 1887-8 he had isolated the poison which he considered to be the disease producing factor by making a glycerine extraction of the cultures. Roux and Yersin³⁶ (1888) reached the same conclusions, using however, the filtrate from seven days old cultures. The ten years following are replete with incident, investigators in Britain and the Continent and in America performing much work. Neisser³⁷ in 1897 described the special staining process which bears his name. Particularly into the question of the virility or length of life of the organism was research prosecuted, and in 1894 at a Congress at Budapest, Loeffler enunciated that "Convalescents from Diphtheria should not be permitted to resume social intercourse until the complete disappearance of the bacilli had been demonstrated by bacteriological examination", and on the same occasion urged the necessity for disinfection.

The immunity and susceptibility of animals also received much attention in this decade, and certain statements particularly those referring to a diphtheria like disease amongst birds, particularly fowls, being identical with diphtheria in the human being were so weighty and apparently well confirmed though actually incorrect that a certain amount of doubt was existent for quite a long period. Up to the present,

however, both experiments and observations would indicate that diphtheria is almost entirely spread by human agency. The few years preceding 1890 were also rich in experiments directed towards a fuller understanding of the nature of the toxins, and attempts towards their isolation.

Contemporaneously Loeffler and Behring contributed much to the subject of the effects of chemical agents upon the life of the bacilli. At this time also Behring and Kitasato collaborated in their serum research in connection with Tetanus anti-serum.

The year 1891 is marked by the publication by Behring at the International Congress of Hygiene and Demography in London, of his paper in which he makes known his discovery of the anti-toxin power of the blood of highly immunised guinea-pigs, that immunity having been attained by way of an artificially produced non-fatal attack of diphtheria. Confirmatory experiments were performed by Fraenkel, Wernicke, Roux and others. From this stage commenced an era of phenomenal changes in the treatment of Diphtheria. In 1893 the preparation of the serum on a large scale was first instituted by Meister, Lucius and Brüning at Hochet on Main.

The year 1894 saw the end of the pre-antitoxin days, by then the serum having become known to most. As time passed its use, however, became more general and its champions more numerous, until now, except in

the case of a few misguided individuals, the treatment of Diphtheria by anti-toxin is the academic procedure. During the seventeen years which have elapsed since its institution many aetiological factors have been brought to light, have been tested, and in many cases have been explained. Similarly many phenomena concomitant with its clinical employment have been noted and discussed, and theories as to their *raison d'être* expressed. Concurrently, the bacteriologist has added to our store of knowledge upon the subject. Larger experience and more detailed knowledge have shown certain dangers, greater or less, which may be encountered in association with serum administration; but these incidents are of such relative infrequency as by no means to be looked upon as detrimental to its value or contra-indicative to its exhibitions provided the precautions pertinent to such dangers are taken. This particular phase will be dealt with more fully in a later Section.

Certain questions relative to aetiology and prophylaxis of particular interest to the clinician.

It has been established as a bacteriological fact that certain people are capable of carrying the Diphtheria Bacillus in the nose, naso-pharynx and throat for long periods without themselves suffering from the disease, but nevertheless capable of transmitting it

to others. Such persons have been termed "Diphtheria Carriers," and their influence in disseminating the disease must be great. Though they do not as a rule show the clinical signs of the disease yet their mucous membrane has been invaded by the bacillus. Some consider that the organism is in an avirulent condition pro tempore, but that, given certain circumstances, it may become virulent, and perhaps produce its pathognomonic effect upon the carrier if he be not immune; or that having become virulent, may be transmitted to anyone with whom the carrier comes in contact.

How to deal with such factors is a very difficult problem, but of equal or even greater import is the question of discovering these cases. A "Bacteriological Census", if one may be pardoned for coining such a phrase, is a practical impossibility. Yet some little might be done by means of a bacteriological survey of school children. I here make a digression to point out a real influence school attendance has upon diphtheria incidence.

I have noticed almost invariably during the vacation periods the number of cases coming to Hospital shows a diminution whilst as a rule within a week or so of the resumption of attendance there is a noticeable increase. Such increase, besides being dependent upon the congregation and co-mingling of those most susceptible, habits and actions bred childhood familiar-

ity and simplicity. "Missed cases" i.e. undiscovered cases of mild rhinitis or pharyngitis of a diphtheritic nature, dust and other causative elements, may in my view, not be entirely independent of the presence of one or more diphtheria carriers.

To revert to the means of dealing with carriers one would certainly ask for their temporary withdrawal from school or home, and their being isolated. In all cases a thorough curettage of the naso-pharyngeal space would be desirable; my reason for this suggestion lies in the fact that I have noticed when bacteriologically examining recovered cases of diphtheria with a view to their discharge from Hospital, that those cases in which the bacilli are unusually persistent and for which great difficulty is met with before obtaining a negative result are usually the subjects of chronic tonsillar changes, adenoids or some similar hypertrophic condition of the nose or pharynx. Regular and frequent douching of the nose with an antiseptic lotion, the direct application of antiseptics, and other means of a like nature might have some effect in clearing away the offending element. The "Missed Cases" recently mentioned too form an interesting class. Mild unrecognised cases have been spoken of already. Rhinitis, of a mild degree with the *Bacillus Diphtheriae* as the causal agent is usually overlooked, due perhaps to the casual observer being unaware of its comparative frequency.

Similarly, the *Bacillus Diphtheriae* has been discovered on very numerous occasions in cases of Post-Scarlatinal Otorrhoea.

The systematic medical inspection and examination of school children now instituted, in most places at least, will, it is to be hoped, have weighty influence in eliminating these latter.

The occurrence of diphtheria of the skin has been recorded on numerous occasions during the past few years. Such a condition, if unrecognised, might be the cause of spreading the disease in a school or family, and therefore its possibility of occurrence must not be lost sight of.

The Charge Nurse of one of my Diphtheria wards contracted a diphtheritic infection of one of her fingers on which there was a slight cut. The course was that of a typical attack of Diphtheria, and during her convalescence she developed cardiac dilatation which was accompanied by murmurs.

General Pathology too, has done much in the last decade or two towards aiding the attainment of better knowledge of many of the questions pertaining to the morbid processes of the disease; unfortunately, however, many of the problems still remain to be solved, particularly those relating to the intimate actions of toxins and anti-toxins, and their effects upon the tissues for which they appear to show special affini-

ties; the untoward sequelae of serotherapy also are among the unexplained problems.

Another interesting phase is shown by the occasional want of accord between the bacteriologist and the clinician. Certain it is that some cases of sore throat undoubtedly proven by bacteriological examination to be positive in regard to the Klebs Loeffler Bacillus, do not in their course, etc., show the clinical features of Diphtheria. Conversely certain acute anginas, etc., present and are followed by a train of symptoms pathognomonic of a Diphtheritic infection yet at no time give a satisfactory bacteriological result. These latter are termed "Diphtheroid" or pseudo-diphtheria yet paralysis may on occasion follow. An interesting case which came under my care was as follows: Catherine K., aet. 5 years. Sent to Hospital as "Diphtheria", admitted on the 5th day of disease. Whitish flaky membrane rested upon each tonsil, which was highly inflamed and swollen. The membrane cleared up in four days under serum and local treatment, but the tonsils became very necrotic in parts and the temperature remained high for a further three days. On the tenth day after admission, marked pulse failure occurred accompanied by vomiting; within 12 hours swallowing became impossible, any attempt being at once rendered abortive by regurgitation. The

condition lasted a further 24 hours, when after a sequence of symptoms identical with those usually seen in cardiac paralysis, the patient died.

Repeated bacteriological examinations did not discover the Diphtheria Bacillus during the entire course of the illness. Clinically the case was undoubtedly one of diphtheria, yet the bacteriological confirmation was entirely unobtainable.

Much has been done towards mastering many of the problems of this malady. Yet there are still some of the riddles to be solved, and it is to be hoped that the morrow will bring with it the knowledge necessary for their elucidation. Such a dénouement would indeed be a crown upon the work originally begun by the faithful observers of days now long past; whose labours formed the foundations upon which has been built the wonderful edifice of the Serum Treatment of Disease.

TREATMENT.

(a) Serum Therapy.

Anti-Diphtheria Serum.

The steps which led up to the discovery of a serum with antitoxic properties in regard to Diphtheria have been cursorily noted in the introductory History in this Thesis.

The mode of preparation of antitoxin, it is not my intention to describe, that matter being one of every day knowledge at this time. Similarly an extensive eulogy of its properties will receive no place here. Such is not necessary, for to even the most casual clinician the profound nature of its virtues are more than manifest.

Great however, as are its good points, yet there are drawbacks to its uses, and limitations to its advantages.

The various disturbing and undesirable sequelae which sometimes result upon its exhibition though happily only rarely, show that this therapeutic rose is not without its clinical thorn.

The extirpation of these unsought and undesired complications of serum treatment is the aim of very numerous observers and experimenters at the present moment and doubtless the morrow will shed much light upon the dark subject of today.

Perhaps also some means will be devised to augment its powers. It is proven to be both curative and prophylactic, that is, it will not only cure a patient who is suffering from an invasion of the specific microorganism in a non-lethal degree, but it will so augment the powers of resistance of a person who has been exposed to the disease as to enable him to successfully exist and ward off an attack of the disease. This immunity is however, short-lived, being only of three or four weeks' duration. When given in the case of established diphtheria its action, provided the patient is not suffering from personal hyper-susceptibility or long duration of the illness overwhelmed with the toxin of the disease is presumably an exhibition of the production of any free or uncombined toxin present in the blood. The combination of toxin and its complementary element in the blood tissues is undoubtedly a most complex and highly stable one, and might be likened in parallel to the persistence of the product frequently when carbon monoxide is inspired into the system and forms a combination with the haemoglobin of the blood. Dissociation or dissolution of the elements is brought about only with difficulty, if at all. Could a serum be produced which would not only be curative and prophylactic, but in addition, have reconstructive powers which would enable it to undo the harm already done by the toxin absorbed before

the actual injection of antiserum, then, indeed would the treatment be an ideal one.

Its effects upon the general prognosis of the disease has already been dealt with.

Yet, nevertheless to this day, voices are on rare occasions raised in protest to its use.

For the section comprising the antivivisectionists there is no satisfactory answer. Their theories and statements based on a foundation of misguided sentiment and leavened with the leaven of wilful ignorance, are accepted only by persons of equally shaky principles. Yet it cannot be denied that their doctrines expressed in public utterance and in leaflets scattered broadcast over the land are bound to have some detrimental effect upon the less thoughtful or educated members of the population. In a printed leaflet which came into my possession recently, I noticed that a case of anaphylaxis was described most vividly and was stated to be due entirely to the injection of antitoxin. Prima facie this might appear to be correct, to the uninitiated. "Post hoc ergo propter hoc" is a line of reasoning, the fallacies of which are too obvious to expect a place here. One cannot refrain however, from expressing the deepest regret that the legal forces of our country are unable to prohibit the dissemination of statements of this and a like nature, as their influence cannot but be a pernicious one, and

their ultimate effect detrimental to the national health and the public weal.

A most interesting result, and one which at the time caused some shadow of disrepute temporarily to rest upon antitoxin has been shown by statistics, to the effect that after its use became general, post-diphtheritic paralysis appeared to be more frequent. The appended table based upon the Metropolitan Asylum Board Hospital's figures will show the point:

Years.		Percentage incidence of paralysis.					
Non-Antitoxin.	1893...	14.3
	1894...	13.2
	1895...	20.1
Antitoxin.	1896...	21.3
	1897...	20.3.

It might be argued to the detriment of the serum and is so to this day, by certain ill-advised persons - from these data that antitoxin actually causes post-diphtheritic paralysis. Such however, is not the true case. Bacteriological examinations have relegated to their proper sphere many cases of tonsillitis and other forms of sore throat which previously have been looked upon as diphtheria; and moreover many cases of diphtheria which without antitoxin would have died, have instead remained alive, suffering from paralysis during the later periods of their illness.

Varieties of Serum.

Antidiphtheria Serum is manufactured by many firms, principally in Europe and America. The mode of manufacture need not be detailed here, and the methods of obtaining it are essentially the same in all the cases. Certain modifications in bulk and form are however worthy of attention. Radically unitage has no relation to bulk or actual volume; generally speaking however, most serum of the "standard" type averages about 400 Ehrlich Behring units per cubic centimetre. This is an important factor, as in circumstances where an unusually large number of units of antitoxin are required to be injected the question of bulk cannot be ignored, e.g. 30,000 units require 75 cc. of fluid.

Certain makers, however, partly for reason of "volume" are now producing a "concentrated" or "high-potency" serum containing up to 1000 units or more per c.c. This gives a much larger flexibility of dosage when considered from this point. Another benefit claimed for concentrated sera is that owing to their being actually less serum proper injected the tendency to serum sequelae is lessened; and I am led by experience of its use to agree in a measure with this contention.

Gibson²⁹ in 1905 found as a result of experiments following on the lines laid down by Atkinson 5 years previously that if antitoxin serum were treated with

Ammonium Sulphate and the resulting precipitate dissolved in saturated sodium chloride solution, the globulin dissolved in this solution contained all the antitoxin elements, freed from the proteid non-antitoxic factors.

The soluble globulins were precipitated by acetic acid and placed in a parchment sac and dialysed. The solution of globulins was then neutralised and sufficient sodium chloride was added.

The results obtained by the use of antitoxin-globulin solutions are stated to be highly satisfactory. As I have had no opportunity of personally testing the product I am not able to express an opinion thereon.

Following the same principle a "dry" serum is now placed at the service of the clinician. It is claimed by its sponsors to be almost without rash producing potential *pari passu* with complete antitoxic powers of unitage. It is a straw coloured somewhat flocculent powder and is dissolved under all aseptic circumstances in sterile water, distilled by preference, I have tried the preparation in a small number of instances and have had no rash or other unsought results. The trouble of preparation and the large possibilities for aseptic contamination of the solution do not markedly give it a place in advance of its fluid analogues.

For the past year or so I have had very numerous opportunities of clinically testing the effects of concentrated serum and my experience leads me to the

opinion that its advantages over "standard" serum are real and valuable, and, were it not for the extra expense, the cost of this more elaborate article being higher as a result of the necessarily increased technical procedures in the production, it would receive my highest possible benison. The passage of time will doubtless remove this financial obstacle, by the discovery maybe of simpler modes of manufacture.

Dosage of Antitoxin.

Professor Chien's well known dictum "Make your splint fit your patient, not your patient fit the splint" might well be modified to apply to Anti-Diphtheria Serum. Rule of thumb can never govern the amount of serum it is proposed to inject. To arrive at even a rough estimate is not possible; certain factors to be considered immediately assuredly govern to some extent one's requirements, but even here the personal factor of the physician exerts a weighty influence. What, to this physician, is an ample amount for a specific case, to another might appear hopelessly insufficient. *Chacun à son goût* would appear to be the ultimate idea arrived at by reading the various published statements in this regard.

Could a means be devised of estimating the degree of toxæmia present in the particular patient before one and an index or factor of resistance be procurable, then would all the difficulties and differences of

opinion be swept away.

For with even an approximate "index of toxaemia" obtainable the desirable amount of antitoxin could then at least be roughly assessed. Unfortunately such a state of affairs does not exist today, and we are compelled to go on in comparative uncertainty. Each one speaks from his own experience and bases his views thereon. Personally my observation leads me towards the giving of large doses, and I am entirely in accord with a recent writer (Goodall, British Medical Journal, Feb. 11th, 1911) who advocates the injection of liberal amounts, and with ~~him~~ I agree that it is a false economy to abstain from a fairly large initial dose. It is certainly preferable to give too much rather than too little. Antitoxin is not a poison, and consequently there is no danger of giving an over-dose. And it is on the principle of making assurance doubly sure that I recommend such initial doses as 8000 units, 10,000 units or more. I have given 30,000 units and repeated the dose twice within 48 hours; but I admit that such amounts must indeed be described as heroic and would only be justifiable in the most extreme circumstances as was the case which received this large amount. Speaking generally, a case of ordinary tonsillar diphtheria should in my view receive an initial of, if a child under 3 years, at least 6,000 units, or if over that age and onwards, 3 to 4,000 units, such amounts as 1,000 units and 2,000 units be-

le A.

le showing results in 547 cases of Diphtheria classified according to
and day of disease on which Serum treatment was commenced.

Day on which Serum Treatment began														Total		Percent age Mortality
1st		2nd		3rd		4th		5th		6th & up				Cases	Deaths	
Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths					
Ages.																
Under 1 yr.	-	-	-	-	1	1	1	-	-	-	-	-	-	2	1	50.0
1-2	1	-	7	1	8	2	7	2	13	5	9	7	-	45	17	37.7
3-4	2	-	14	1	6	1	2	1	1	1	13	4	-	38	8	21.0
5-10	4	-	6	-	5	1	18	4	14	1	16	3	-	63	9	14.2
11-15	3	-	8	-	8	-	14	2	9	2	16	3	-	58	7	12.0
16-20	5	-	28	-	32	-	33	5	39	7	45	4	-	182	16	8.7
21-25	2	-	14	-	13	-	12	-	7	1	29	2	-	77	3	3.8
26-30	-	-	8	-	5	-	3	-	3	-	8	-	-	27	-	-
31 & up	1	-	19	-	12	-	9	-	1	-	13	-	-	55	-	-
Total	18	-	104	2	90	6	99	14	87	17	149	23		547	61	11.1
Percentage mortality	-		1.9		6.6		14.3		19.5		15.3				11.1	

ing reserved for the very mildest cases, or those about whom only a suspicion is held. This statement, is, at most, only loosely applicable and the following factors must be considered, individually and collectively in making a decision.

- (a) Age of the patient,
- (b) Duration of illness,
- (c) Situation and extent of lesions,
- (d) Degree of toxæmia, or apparent constitutional effect on the patient by the disease.

(a) Age of the patient.

A reference to Table A. brings out two facts in relation to age; the first, that under one year, diphtheria is by no means common, and secondly that it is particularly prone to attack those of from 1 to 5 years of age and that the outlook is the most gloomy for those in the second and third years of life. A further inference can be drawn to the effect that under 20 years of age the fatality of diphtheria approximately varies inversely with the length of life. It might be stated generally, that a good principle to work upon is to entirely reverse the Posological rule for age correction usually employed in regard to drugs and therapeutically. Children require much more antitoxin than adults. It has just been shown that they are more susceptible to the disease and to the effects of the toxins. And by reason of their tender years their

ble B.

ble showing mortality from Diphtheria, classified according to the day
disease on which serum treatment was commenced,

Day of disease on which serum treatment began.

1st	2nd		3rd		4th		5th		6th & up		Total	
Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
-	132	2	137	11	133	21	111	22	175	42	711	98
1.5		8.0		15.7		19.8		24.0		13.7		
Percentage mortality.												

general powers of resistance are naturally less strong. Moreover their proneness to laryngeal involvement demands that the disease be arrested at the earliest opportunity and as completely as is possible.

To give an example, a child of 2 years and a boy of 15 are admitted each with a small patch on one tonsil, and both coming in early and on approximately the same day in regard to date of disease; the child would receive at least 6,000 units of antitoxin and this would be repeated within 20 hours or so if the arrest were not well marked, whilst the boy would receive 2,000 units or 3,000 at most.

(b) Duration of disease.

This is a very important factor and bears much weight upon the efficacy of treatment and consequently the prognosis of the case. (See Tables A and B.) Were all cases of diphtheria discovered and treated on the first day of illness, the mortality would be reduced to a very small amount, and the cause of great discussion upon the topic in hand be to all intents and purposes removed. Unfortunately such is not so; in fact if only by reason of the comparatively insidious onset of the illness and freedom from great discomfort on the part of the patient in the earliest stages, coupled with the tender age of many of those attacked, circumstances would seem to lend themselves to helping a firm establishment of the condition before it can be

discovered.

The influence exerted by the day of disease upon the outlook of a patient is increasingly and progressively depreciative as time passes; and the amount of serum required increases at even a greater rate of progression. In fact, it has been stated that after the fifth day of disease antitoxin is valueless per se; or in other words that the harm done is complete as far as it goes by that time. Whilst not by any means agreeing with either the statement of the inference implied, one is bound to admit that the prospect of a severe case coming under treatment not before the fifth day, is by no means an encouraging one, yet it is obvious that a mild case coming under treatment not before the fifth day cannot be in the way of having a severe attack, or symptoms concomitant with severity would have manifested themselves ere this. I have seen marked cases admitted at a later day, and treated with large doses of serum, do well, but unfortunately these are exceptional and the opportunities of studying those where the result has been otherwise have been far more numerous in my experience. The following are examples:

Matthew D. æt. 26. Admitted on the sixth day of disease with membrane thick and extremely foetid, on tonsils fauces uvula and soft palate. 30,000 units injected, and the same dose repeated in 16 hours, rou-

tine syringing ordered. Throat not clean until twelfth day of disease. Slight palatal paralysis from 31st to 40th day. Result: Recovery.

David East. 24. Admitted on sixth day of disease with membrane formation practically parallel with previous case. 30,000 units injected; repeated in 12 hours, and again in 24 hours. No obvious result; toxaemia gradually supervened, and patient died on the 11th day.

No hard and fast rule can be laid down, nor can any mathematical series or rate be followed in an attempt to arrive at a decision. I am led by my experience to look upon the third day as being "doubtfully safe" and the fourth day as "unsafe", and the succeeding days as "dangerous". Such degrees, however, are best theoretical and essentially nominal, as one patient may be gravely toxic by the third day whilst another might be comparatively trivial on the fifth.

For a given case of ordinary degree I would certainly recommend an increase of at least 2,000 units for each day of disease after the second increasing the proportion for younger children and decreasing at a more rapid rate for older patients. (Ref page 1496.)

(c) Situation and extent of lesions.

Great as appeared the moment of the "day of disease", this element must be reckoned with even more care. At the same time one must reiterate that the

general rule can only be applied loosely to the individual case. It is essential to remember the great tendency towards laryngeal involvement in young children, and I invariably aim at erring on the "too much" side in arriving at the dose for a child, even though only a slight tonsillar lesion be present at the moment. A case coming in with membrane on one tonsil at an early stage might have 4,000 units. Should the day be late the presumption may be made that the case is not potentially bad and hence the dose need not be markedly increased. Both tonsils showing formation of membrane would justify an increase to 6,000 or even 8,000 units; whilst if the faucial arch and the uvula are invaded the latter amount in my opinion constitutes minimal dose. Further involvement of the soft palate demands, I have found, at least the same amount, if not ten thousand units.

Pharyngeal (i.e. tonsillar faucial etc.) deposit with laryngeal involvement is usually due to extension downwards from above and is invariably serious, and I do not hesitate in giving 10 or 12,000 units to such cases, and ordering a repetition of the dose in 20 hours or so if improvement is not manifest.

Similar lines may be laid for those cases showing primary tonsillar, etc. membrane with infection of the nose as a secondary condition.

A point which must not be overlooked is that there

may be extensive membrane formation in the naso-pharyngeal space without much deposit being visible, i.e. on the tonsils, etc.

Purely nasal cases are of two types. The chronic rhinitis indolent in nature, and showing only a thin scanty rhinorrhoea containing Klebs-Loeffler Bacilli does not call for a large amount of serum, if any at all. Such a case is of more importance from the prophylactic point of view than the purely sero-therapeutic. Acute Nasal Diphtheria, however, is of grave import and demands a large amount of serum, 10,000 units being a minimum dose. If the case is received comparatively early, with only a serous or sero-purulent discharge the demand is relatively less than in the stage of purulent irritant discharge with visible membrane in the nasal cavities and marked excoriation of the nares and adjacent lip.

In either stage, the case is nevertheless severe, and I cannot hesitate in pronouncing for a large initial dose with an early re-injection of a correspondingly liberal amount.

In laryngeal cases, by which is meant those cases in which there is no apparent lesion above the larynx, it has been my constant procedure, never to give less than 10,000 units as the initial dose. The case which arrives with a history of laryngeal symptoms of even only a few hours duration and with, perhaps simply a

croupy cough, without any inspiratory recession or loss of "colour" requires a good dose of serum. The possibilities present in the laryngeal form of Diphtheria, leading towards increase of the urgency of the dyspnoea with its attendant strain upon the heart, are so great and ever attendant that the aim of treatment must be constantly directed towards arrest in as prompt and efficient a manner as possible. If symptoms of croup have lasted over more than 48 hours I usually inject 16000 units.

Repetition of the dose within a few hours is the keynote of success in laryngeal cases.

Diphtheritic injection of other parts must be treated according to circumstances. Many, in fact, are not discovered at all and hence receive no serum.

(d) Degree of Toxaemia.

This, in my opinion, constitutes one of the most forcible of the elements involved in arriving at the dose of antitoxin to be given. This patient may come under notice on the third or fourth day of illness and present unmistakable evidence of an almost hopeless condition, whilst the next, arriving on the fifth or sixth day, presents good pulse, red lips, and a general air of comparative well-being. The personal equation of the patient is the pre-dominant factor throughout this section. The signs of toxaemia, a pale almost

transparent waxiness of the face and lips, sighing, yawning, sometimes a hiccough and a general listlessness or drowsiness of manner and a small atonic pulse point to an inundation of the patient by ^{the} toxins. The chances of any good result from serum in such a case are indeed remote. Nevertheless on rare occasions such patients have recovered, and these few instances are sufficient to render it imperative that one should grasp even at the most slender chance, provided the patient is not absolutely "in extremis." It is cases of this kind that I am inclined towards what are termed "heroic" measures. Twenty or thirty thousand units repeated again and possibly again may be justified, and the primary injection may in the light of the results obtained by Cairns, be given intravenously.

Thirty thousand units constitute the largest single dose I have given; there are writers, however, who aver to giving much larger. They have, no doubt, had justification, but, greatly as my personal taste leads me to favour the liberal hand, yet I am of the opinion that as much good is obtained from thirty thousand units as from sixty or more thousand in these extreme circumstances.

Sometimes the question arises, is it justifiable or worth while to give serum? And the answer is sometimes difficult to supply.

The following case may be quoted. James S. æt.

20 months admitted on the eighth day (approximately) of disease. On examination membrane was seen to extend over tonsils, fauces, uvula, and soft palate, and laterally on to each cheek coming forwards almost as far as the aperture of the mouth. The patient was pale and waxy in face, the pulse almost imperceptible, and the hands cold and the foetor from the mouth was extreme. No serum was given, and the patient died within a few hours.

This is one of ten such cases which have occurred in my experience.

Adenitis (cervical) of a certain type is not uncommonly met with in marked cases and when present may be looked upon as a token of severity. In septic or anginous scarlet fever the inflamed glands in the neck are enlarged, and the neck presents a tense, brawny, "blae", (to use a Scot's phrase) appearance, the whole mass being fused together and the surrounding tissue congested and angry. In Diphtheria, however, the appearance is vastly different. The glands when involved are swollen but remain separate; whilst being tender to touch, there is no angry appearance; and the adjacent tissues are not affected, but remain pale. The appearance of a child with marked adenitis in diphtheria is very characteristic and the rounded swellings under the jaw and the fat neck have been described by

the title "le cou proconsulaire". Foetor too in my opinion, is an undeniable sign of severity. The insistent and peculiarly sickly and offensive glue-like odour found in severe diphtheria is, to my mind, pathognomonic and symptomatic of the disease, and it usually signifies a high degree of infection.

Haemorrhage from the mucous surfaces of the mouth, nose, or from the intestinal tract, must always be viewed with the gloomiest forebodings. Slight haemorrhage on stripping or loosening a patch of membrane is of no consequence. But the oozing from the nose, tonsils, or gums, the occasional expulsion of larger amounts from the stomach, or via the intestines as shown by tarry or sanious stools, all point to a supreme and overwhelming toxæmia.

An exceptionally severe case which came under my charge was as follows:

Gladys P. æt. 9, admitted to Hospital on the 6th day of disease. On examination there was found dark bloodstained membrane on both tonsils, the faucial arches, uvula and soft palate. The foetor was most pronounced. The nasal cavities were filled with dark blood clots, and there was haemorrhagic oozing from the gums. A few petechiæ were present on the abdomen, and the liver showed slight enlargement. 30,000 units of antitoxin were injected, much subcutaneous haemorrhage marking the sites of injection. Other

treatment included the intramuscular injection of 20 c.c. sterile gelatine. At the end of 12 hours the haemorrhage appeared to abate but 6 hours later there occurred a profuse haematemesis. Bloody vaginal discharge was also noticed. Thirty hours after admission the child, who was meanwhile comparatively rational and clear in intellect, said that she could not see with her left eye. Six hours later she cried out that she had gone blind and was unable to see anything at all. From that time she became restless, and thirst, a prominent feature throughout, more urgent. Sanious vomiting continued for a further 8 hours, when, suddenly complaining of abdominal griping, the child with no warning died.

Post mortem examination revealed innumerable petechial haemorrhages in the lungs, pleura, liver, intestines and spleen. The left ventricular wall, and to a less extent the right also, was altered to a black currant like jelly mass. Dissection of the eyes showed in each case the retina suffused with a large haemorrhagic patch, with, in the case of the right eye extravasation into the posterior chamber.

The exceptionally severe nature and the unusual eye symptoms seen in this case, form my excuse for introducing it at this stage.

Not all haemorrhagic toxic cases are as marked as this; in fact, I have been unable in the records av-

ailable to me, to discover its like. None the less, haemorrhage must always, in all cases be looked upon as an omen of the gravest import. Incidentally, one might here remark that this statement applies equally to all the "Infectious Fevers" whether shown in the exanthem or in the localities of infection.

Two other factors which my experience has impressed me as being of value are: (a) Family or constitutional predisposition. In regard to Diphtheria particularly, I have noticed a marked "family" strain. If I find in the history of a case that at some time previously, maybe independently of this present attack, one or more numbers of the family have died of diphtheria, I am inclined to weigh this in the balance as against the patient and I increase serum accordingly. This family susceptibility cannot be read as a rule absolute by any means but nevertheless my observations have been such as to lead me to look upon it as worthy of consideration. (b) The other item referred to rests in race. I have found that Jews are peculiarly intolerant of Diphtheria. What, in say and English child amounts to a relatively mild attack, in a Hebrew child might be followed by quite an unexpectedly adventurous course. As tracheotomy subjects I have received many disappointments from the race, and as ordinary cases of simple type found them particularly prone to circulatory weaknesses.

The raison d'être of these two conditions I am quite unable to supply; perhaps that which horse breeders call "stock" or "strain" exerts an influence or perhaps simple coincidence has led me to attach undue importance to the circumstances.

Repetition of injection of Antitoxin.

This is a question upon which the clinician must be guided by circumstances. If the desired effect is brisk and early in appearing, and the case was not severe when it was received, then the serum need not be repeated. But if the reaction is tardy and the symptoms show little diminution then a further dose is required.

Laryngeal cases, speaking generally, require a second, and even a third re-injection; and if the dyspnoea shows no signs of decreasing within 10 or 12 hours, such a course is demanded. In those cases which have pneumonia or broncho-pneumonia, antitoxin I have found, appears to have a decided beneficent effect and consequently,^{and} I am in favour of repeated injections. The severe forms with membrane extending downwards into the trachea and bronchi require a great deal of antitoxin. I have found as a rule that the generous administration of serum to cases which have required tracheotomy is the essence of success in removal of the tube; I usually take out the tube at the end of 36 hours and, provided that the case is well

under the effect of antitoxin, the child is, as a rule, able to completely dispense with it.

Maximum dose of Antitoxin.

Many writers state their ideas as to a limit of the amount of serum to be given. Personally I am unable to do so, as I believe that no boundary line can or should be drawn. The maximum dose is that amount which for any given case will completely produce the clinical effects pointing to an efficient readjustment of the damage due to the particular affection.

The modes of administration of antitoxin will receive notice elsewhere.

Antistreptococcus Serum.

Whilst speaking in reference to Sera, a note may here be made of the value of coincident administration of Polyvalent Antistreptococcus Serum with Antidiphtheria Serum.

In those cases which present what is termed "mixed infection", i.e. a streptococcal inflammation superadded to the genuine diphtheritic invasion, I have found the serum of great use. The necrotic inflammation of the tonsils, with high temperature and septic absorption causing local adenitis, or the dirty sloughing ulcerative conditions observed in some "septic cases", after the diphtheritic membrane has cleared away, are wonderfully helped towards a cure by Antistreptococcic Serum. I usually give a single dose of

15 to 20 c.c. hypodermically, and this has usually proved an adequate amount, a repetition of the amount being required only in the very severe conditions.

During the last nine months, I have tried on many occasions the subcutaneous injection of a polyvalent streptococcus vaccine of a strength of five million cocci per cubic centimetre. Equally satisfactory reaction has been obtained from this method.

(a) Adjuncts to Serum Therapy.

1. General Management.

The philosophy of Hilton "The apostle of Rest", could apply to no condition with greater claims than to Diphtheria. Rest of body, and of mind as far as is possible, is in my opinion the dominant note throughout. The patient should be kept absolutely prone for at least a week, no pillow being allowed until this period has elapsed. The disease, from beginning to end, is of such a markedly depressing nature that even in the case of little children, very little difficulty is experienced in keeping them lying flat. Then, provided the pulse has maintained a fair tone, one pillow may be given, for use during the day only. I rarely allow my diphtheria patients to have a pillow during the night until the end of the third week. All this is with a view to giving the heart as little work as possible beyond the amount necessary for the simple

propulsion of the blood through the recumbent body, by the elimination of the force of gravity as nearly as can be approached. The room or ward temperature should not be below 60° F., and ventilation should be free. The various aspects of the pulse should be noted, particularly as to rate and rhythm, and the tone, as shown by the rise and fall of the wave, at regular intervals of a few hours duration. The pulse of the few hours succeeding midnight is of notable value as this gives us an estimate of the patient's condition at its worst in the daily cycle. Tachycardia or bradycardia may occur; neither of these alterations in rate is a good sign, and of the two I have found that bradycardia is the greater evil. Alterations in rhythm usually take the form of intermittency or irregularity. Both of these variations are indicative of circulatory weakness and call for rest and appropriate treatment; but irregularity of the pulse, in my opinion, is distinctly the more serious, particularly if marked alteration in rate be present also. Similarly the occurrence of valvular changes, or variations in the area of cardiac dulness must be watched for. The heart and general colour having remained satisfactory the patient at about the 16th to the 18th day may be allowed, by gradual propping up by means of pillows or bed rest, to sit up in bed. during the day, and by the 21st day or thereabouts he may be permitted to get up. Thereafter

gentle exercise in the open air is beneficial. Anything suggestive of strain must be rigorously denied owing to the "softened" condition of the heart muscle and the consequent tendency to failure, dilatation, etc. Vigilance must be strictly maintained throughout convalescence in another direction also. The onset of paralysis is sometimes discovered early, by the observation of certain small incidents. Palatal paralysis, the commonest of all the grosser paralysees, is usually discovered by the regurgitation of fluids when the patient attempts to drink. A much earlier sign, however, which I have found to be quite frequently present consists of a little cough on drinking. The patient usually ascribes it "to something going down the wrong way." It is due, I am inclined to think, to weakness or preliminary partial paresis of the soft palate, which whilst still retaining sufficient power to swing backwards to a partial extent cannot completely perform its office of barring off the upper or nasal portion of the naso pharynx. Similarly, the common speech of the patient may disclose palatal weakness. "Good morning" is a useful phrase with which to test the speech, and possesses the advantage of being an every-day expression.

Cardiac trouble is often heralded by the act of vomiting. Incipient paralysis of the legs may sometimes be disclosed by a slight catching of the toes on

the floor, as the patient walks; or he may stumble. Undue tendency to lifting of the feet, i.e. slight high steppage gait should always demand investigation. The eyes must be watched for slight squint. Laryngo-pharyngeal paralysis is frequently first declared by a peculiar cough, lacking in the explosive element. Such are the usual forewords, so to speak, of the various paralyses, and their early discovery enhances the value of treatment. The nurse in attendance, it will be seen, must be constantly on the qui vive from the beginning to the end, so pregnant with possibilities, some indeed of sudden and grave import, is the disease.

As a rule at the expiration of five weeks the patient has sufficiently recovered to commence a gradual resumption of his normal mode of life; and, granted that he is bacteriologically "free", this step may be taken.

The diet throughout should be liberal. I am in the habit of allowing food whenever, within reasonable limits, a patient desires it. Even when the membrane is not yet gone from the throat, I have no objection whatever to his having moderate amounts of milk puddings, egg-flip, boiled eggs (soft) or even thin bread and butter. Soup, and meat extracts may be given in full amounts. As soon as the throat is clean, the dietary scale may be increased as quickly as is commensurate with the patient's powers. Contrary to the

rule in scarlet fever, albuminuria, even when pronounced does not form an indication in my view, to marked curtailments of the dietary régime. Alcohol, I am convinced is a most valuable asset in the treatment of this depressing malady. Wherever there is shown any want of tone in the circulation, the giving of brandy or good whisky is of decided advantage. A young child of 2 years or so is easily able to take an ounce of brandy in small quantities at intervals, in the 24 hours.

Port wine is an excellent aid to tonic treatment in convalescence. I have tried some of the advertised wines which contain meat extracts, but have not observed any advantage in them.

2. Local Treatment.

Local applications to the throat were, in the pre-antitoxin era the main weapon of the physician in combating the disease. And today they still take a large part as auxiliaries to serum therapy.

The mouth etc. in all cases must be kept as clean and as free from mucus etc. as possible. Solutions of various kinds, all essentially antiseptic and usually anaesthetic and astringent in action, are used by many for direct application to the local lesion. Of these, Loeffler's Solution containing tol^uol and menthol dissolved in alcohol with either Liq. Ferri. Perchlor. or Creolin, is the best known, and good results

are claimed for it. The caustic and irritating "paints" of elder physicians are no longer employed. Other substances employed include carbolic acid, tannic acid, lactic acid, potassium permanganate, sodium sulphate, iodine solutions, chloral hydrate, boroglyceride, etc. and have been used singly or in combination with one or more similar agents. Most of them are efficient but their effects are purely local, and certain of them may impair the vitality of the local tissues.

An application composed of Carbolic Acid, Tincture Ferri. Perchlor. and Glycerine is of use in the necrotic and septic types of angina as also is the application of pure *Hydrogen Peroxide*. *I have employed the* direct application of antitoxin to the tonsils, etc. but have not observed any marked benefit.

Various drugs in solution, or oily suspension are favoured for use with sprays or atomisers. These are mainly palliative. Adrenalin solution (1-1000) is a spray solution, I sometimes employ in routine treatment, and then only when there is a tendency to slight oozing of blood, when the membrane is being cast off. Hydrogen Peroxide solution is occasionally of value as a spray in decreasing the offensiveness of a septic anginous condition. Of all the local measures employed however, I place great faith in syringing or douching of the mouth and throat. This may be accomplished by means either of a douche can and tube, or by using an ordinary four ounce size ball syringe.

The procedure is infinitely superior to gargling, this latter being impossible in the case of young children, and not always possible with some adults, and is highly gratifying to the patient. All the diphtheria cases under my care are regularly syringed every four hours until the throat is clean. The solution most usually employed is Lysol (3I. ad OI) or Liq. Carbonis Dertergens (or Liq. Picis Carb. P.B.) in the same strength. With the patient lying on his side, the mouth, tonsils, etc. may be syringed with ease. The Lysol solution is the orthodox one in this Hospital. The special advantage of the "Carbonis" solution is its high deodorant property, the odour from a foetid throat being removed or decreased greatly after a very few irrigations. The nose may be douched similarly. I must confess, however, to a less easy mind in regard to nasal irrigation. Some patients do not lend themselves to the process at all well, even to the most gentle and careful mode of procedure, and the disastrous effects which may follow a struggle with a diphtheritic child are too serious to deserve anything but a severe avoidance. Consequently, except for the external toilet, I am inclined to forego douching of the nose, and trust in the specific action of large doses of antitoxin resulting in local improvement.

Other solutions which may be employed as irrigants include, chlorine lotion~~s~~ of variable strengths,

Boric Acid, Sodium Chloride, Potassium Chlorate, Sodium Bicarbonate, singly or combined, of a general strength of 3I ad 0I.

Some physicians have expressed faith in inhalations of steam, alone or medicated. Personally I have not seen any particular benefits from these in lesions of the mouth or nose, and therefore do not advocate their use in this instance. In the laryngeal cases, however, I find them of distinct value and they will receive notice when such cases are discussed later.

Constitutional Treatment.

Is directed mainly towards keeping up the patient's general strength and the prevention of circulatory depression and the avoidance of paralytic tendencies.

The first and foremost of all tonic drugs in Diphtheria is Strychnine, and its use in this Hospital is continuous throughout the entire course of the disease. Combined with Tincture Ferri. Perchlor. and occasionally Phosphoric Acid Dil., it forms the "stock mixture" for all the diphtheria patients. Given carefully pro rata with age, one has only twice seen untoward symptoms, and these were only of a temporary nature, and undoubtedly from circumstances, the result of the patient's personal idiosyncrasy. Formic Acid in 25% solution, as recommended by Ker and Croom,⁴⁰ is also a highly efficient tonic. It receives further mention in

connection with Paralysis. Rolleston has stated that Adrenalin forms an excellent tonic in Diphtheria. I have not found it better than Strychnine as a general agent. Per rectum with normal saline however, I consider that it is invaluable in cardiac failures. Digitalis, though deprecated by some writers, has recently been recommended by Tissot⁴¹ as a cardiac tonic of special value in helping "the oxidation of toxins" by augmenting the circulation.

The various Phosphates, Glycerophosphates, Hypophosphite tonic syrups are of value. A word here may be inserted as regards aperients, castor oil, and confection of sennas are in my opinion the best. Diphtheria patients are unable to tolerate the more severe laxatives.

Special Treatment.

Cardiac Complications.

These may be simple (by comparison) or severe; of relatively slow onset or with remarkable suddenness; and may be the direct result of the morbid process upon the heart tissues itself or the effect of the toxins upon the nerve supply to the heart.

There is no other disease in which symptoms of heart failure occur so suddenly and unexpectedly, and there is perhaps no other disease in which physicians are so often deceived in the matter of prognosis. By far the commonest cause of death in Diphtheria is card-

iac failure, and this sequel is particularly prone to happen during two distinct phases of the course. The first phase is during the earlier stages of the illness. The patient is admitted in a toxic condition; in other words his blood and tissues are impregnated with the morbid products of the bacilli. Pathology has shown that this toxin produces a marked degenerative change in the cardiac muscle, and to a less extent at this stage, the nervous system. The patient on admission is pale, waxy and listless; the pulse is small and somewhat collapsing. Sighing and yawning may be noticed. The mind is clear in some cases to the end. Retching, or perhaps actual vomiting may be present, even water being rejected by the stomach. Thirst may nevertheless be marked, and the constant desire for, and attempts to swallow fluids with the almost immediate return, may be a lasting feature. The hands and feet become colder and colder. Restlessness may also be pronounced, the child throwing its limbs from under the bedclothes. Fear is usually also a prominent symptom, particularly a marked dread of being left alone. The condition progresses thus, until perhaps without any obvious cause or warning, a syncopal attack takes place, which may at once be fatal, or the patient may recover, only, however, to die in the next or other succeeding attack.

The pale yellowish white face with the sunken dark eyes and anxious expression, the restlessness of

body, the sighing, and the clearness of mind, all combine to make a characteristic picture.

Praecordial pain or anxiety may be complained of; sometimes, it is not a marked symptom.

I have noticed, however, on not infrequent occasions, the terminal syncope has been immediately preceded by abdominal pain or griping accompanied by an urgent desire to evacuate the bowels.

Treatment of this ^{cardiac} condition is mainly palliative, and little can be expected of it. The foot of the bed should be raised and the general warmth be kept up. Stychnine, alone or in combination with Nitroglycerine is given hypodermically, or oil camphorated, may take its place. Both are excellent stimulants, and the camphorated oil possesses the advantage of being better borne. The subcutaneous injection of ether, etc. is another cardiac stimulant, though its action is comparatively evanescent. In the cardiac failures, I have had very gratifying results from Adrenalin given by rectum. By the mouth I have not observed its results to be nearly so encouraging. Children can tolerate large doses, XV m. being an ordinary dose for a child of say 3 or 4 years, and this may be given every four hours for quite a number of days. I usually give it in about 4 or 5 ounces of normal saline solution, I may add half to one teaspoonful of brandy. This method is one of the main lines of our treatment of the

grosser cardiac depressions.

Nutrient enemata of Peptonised Milk may be used also and to these a little Valentine's or other meat extract may be added.

Commonly, however, rectal medication is impossible by reason of the inability of the patient to retain. In these cases hypodermic aids are alone practicable. The second or later "period of cardiac depression" as it is termed by Caiger, is usually met with between the 14th and 35th days of disease. It may arise earlier, and rarely later. The condition whilst to some extent resembling in its symptoms the previous type is nevertheless largely dependent on a different cause. The depression of the first period, it was suggested, was due to a condition of intoxication and its direct effect upon the cardiac muscle. Whilst in a measure, contributing to this later form, the heart muscle is not the major factor. We have, by the end of the second week, arrived at the stage of the disease when the neuritis and the characteristic resultant paralysis may be expected. And it is this neuritis affecting the vagus nerve, which, it is believed by many, is the primary agent. Personally I am led by observation to agree with this explanation.

The condition may be sudden and unexpected in its onset, and the patient be dead in a minute or two as a result of a syncopal attack. E.G. A little child,

admitted originally as a laryngeal case and tracheotomised, had after an otherwise uneventful course reached the 42nd day and was up and about in the ward. Whilst sitting with other children, he was seen by the nurse to suddenly drop his head and roll forwards. After only one or two sighing respirations the patient was dead.

Or the course may be ^{of} only one or two hours duration, and may occur in patients whose condition on arrival was not such as to justify a gloomy outlook.

Rebecca M. æt. 6, admitted on the 4th day with membrane on one tonsil. Received 8000 units hypodermically. Throat cleared up well and promptly. In bed 14 days and allowed to get up. Lively and bright and of good colour throughout. On the 20th day at 7 a.m. the patient vomited and the pulse markedly failed. Hypodermics of Strychnine and Saline and Adrenalin enemata ordered. Vomiting continued and a syncopal seizure at 9.20 a.m. resulted in death.

Sometimes however, the fatal issue is preceded by symptoms which spread over 2 or 3 or more days. There may be no warning changes in the pulse etc.; an attack of paralysis; an attack of vomiting with some retching first drawing particular attention to the patient. Praecordial pain or anxiety is commonly met with but in some cases is not always a prominent symptom. Or in some cases the pulse may become irregular

and weak, or the rate may show alteration, often as a slowing. Or an attack of paralysis elsewhere may gradually merge into cardiac paralysis. The first two modes of onset are however, the commoner. The retching if any is soon replaced by actual vomiting and at the same time the pulse becomes weak and atonic. The patient is pale, and the intellect clear. At this stage the hands and feet are warm.

The foot of the bed should be raised and the patient have his bed placed near the fire. Now is the time which I have observed to be the most favourable for the warm saline and adrenalin enemata with or without brandy; and their effect is distinctly enhanced in some cases by the inclusion of full doses of Formic Acid, 20-30 m. of the 25% solution commonly being used. I particularly mention "some cases" as I have observed that Formic Acid acts, or is at least much influenced by personality. Some cases react remarkably well to it whilst others give no response to it at all. It is stated that a period of 48 hours elapses before the therapeutic action of Formic Acid is noticable. This may be so when it is given per os, but I am very much inclined to the belief that its action is much sooner evident when given per rectum. Coincidentally hypodermic injections of Strychnine or better still strychnine with nitroglycerine, or of camphorated oil, etc. are to be commenced. Brandy in warm milk, water, or

soda water may be tried by mouth. Milk and perhaps meat juices, in very small sips at frequent intervals may be tolerated also. But frequently, even sips of water are not retained. In such cases rectal feeding must be begun. The peptonised milk enemata previously mentioned, have given me the best results in this direction. The three points essential in treating these cases with any hope of success are: firstly, take every possible means to preserve the body warmth; secondly, keep the head low, and the foot of the bed raised; and thirdly, commence the saline and adrenalin enemata at the earliest opportunity. The earlier the commencement of rectal methods the greater the chance of recovery; for later the sphincters may become inoperative and the rectum as a result be unable to retain the fluids, and when this occurs, obviously the treatment is impossible. I feel able to speak deliberately on this particular matter, as on many occasions since we commenced this method, nearly three years ago, many cases have recovered which in my earlier days would undoubtedly have died, when we pinned our faith in hypodermic injections alone.

Adrenalin appears to support and steady the heart and maintain its tone. Any tendency to increase of blood tension as a result of its injection is corrected by nitroglycerine. The virtues of strychnine are too familiar to require description, and the warm sal-

ine solution is distinctly a stimulant of recognised merit. Whether this line of reasoning is correct or not I do not argue; but the results obtained are quite sufficient to justify and even demand the methods enunciated. I may here again state that adrenalin appears to be very well borne by the young patients usually treated. A child of six may with safety receive XX minims in the enemata for a number of days.

Should the patient not respond to treatment, then indeed is the prospect a gloomy one. The vomiting becomes more frequent, and renders the taking of food or drink practically impossible. Thirst and restlessness too become more pronounced as the case proceeds. I have found that nepenthe, given carefully in doses of 1 or 2 minims, if retained, gives some slight relief to this restlessness. The patient sighs and yawns frequently. Gradually, perhaps at times fairly rapidly, the patient lapses into the condition described just previously. Other paralyses may appear. Not uncommonly palatal paralysis with its concomitant regurgitation is superadded. The intellect, in practically all of the cases, is quite clear and rational till the end. The case usually terminates by fatal syncope. The same abdominal pain mentioned in the earlier type is not any less common in this.

In dealing with the comparatively minor circulatory disturbances such as slight alteration in tone or

rhythm, I have found, contrary to the experience of some writers, *strophanthus* to have a value in steadying the heart, and, combined with strychnine, has given satisfaction. In rare instances it secures labor.

Rest in the prone position is however, a sine qua non, and I am assured, contributes in no small way towards cure. A not uncommon symptom, at times very significant is an undue accentuation of the second sound with an alteration in its quality. Instead of "Lub-düp", we get "Dub-dub" the two sounds showing less difference than normally, in space and in character, and assuming something in the nature of a "tramp, tramp" time. Rest is the line to follow.

Dilatation and bruits, particularly a mitral systolic murmur, are not rare. Strain or over taxing are usually the causal agents and must be eliminated.

It has been far from uncommon with us to find an abrupt and at times alarming pulse failure as a result of the sudden and extensive appearance of Urticarial Serum rash. This may be due to the rapid depletion of the blood of much of its fluid contents by the formation of the skin lesions.

(c) Post-Diphtheritic Neuritis and Paralysis.

The paralysis is a definite peripheral neuritis, and is consequently a lesion of the lower neurons. Sometimes forms of it occur during the first week, but such "precocious" paralyses are exceptional and when

met with form an omen of bad import. The end of the second week is the common period, but the complication may arise at any time from ten to twelve days up to two months. In rare instances it occurs later.

The following case is illustrative:-

Doris C. after a severe attack of Diphtheria involving tonsils, fauces, and soft palate, had a very satisfactory course. Except for palatal paralysis, mild in type, and which lasted for only 13 days, her convalescence was surprisingly good. After nine weeks detention in Hospital she was discharged to her home. Seven weeks after this or 16 weeks from the original lesion she developed a marked squint which persisted for two months.

Whenever there is paralysis, however slight the patient should be confined to bed, because whenever it is present, the danger of cardiac involvement^{is} also attendant. Paralysis of the soft palate, in which the curtain hangs limp and anaesthetic (on very rare occasions only one half it is involved) is the commonest of the non-fatal forms. It may commence very early, but most commonly arises about the 12th day and onwards. There is cough on drinking first, and ultimately swallowing is impossible owing to the fluid regurgitating through the nose. Articulation is affected considerably by the escape of air through the nares and the "nasal" speech is very characteristic of the condition.

Food may enter the larynx and trachea and cause pneumonia. The oesophageal or rectal tube may become necessary for feeding the severe cases. Paralysis of the lower limbs is, in our experience, ^{as a result in order of frequency} in rare instances it is complete but generally is only ^{partial} ~~palatal~~. There is usually loss of knee jerks and some muscular wasting. The patient inclines to the broad base in walking. Sometimes there is a tendency to foot drop with the result that the child shows a slight degree of high steppage action. Abnormalities of sensation, tinglings, numbness, etc. have been noticed. Its onset as a rule is rarely before the 4th week; and its course may be of fairly long duration.

Involvement of one or more of the extrinsic muscles of the eye is common, the most usual muscle affected being the External Rectus. The squint may appear suddenly or its onset (generally about the 35th day or so) may be gradual. Paralysis of the ciliary muscle causing loss of power of accommodation, is usually bilateral, and is perhaps more common even than supposed, difficulty in diagnosing the condition in young children preventing its discovery to some extent.

A multiple paralysis is not uncommon and generally occurs at about the 4th week or so. Commencing with the palate usually, it may include the eye muscles. Weakness of the legs with loss of knee jerks, and per-

haps paraesthesia or anaesthesia, may lead to complete loss of power. Involvement of the pharynx is usual in this form, and the cough resulting as previously stated is very characteristic. The expulsive factor is available, but owing to the inability to fix and close the glottis, the explosive element is lacking, with the result that the cough is slow and straining. Collections of mucus is a live danger at this stage, and must be prevented by posture or douche or drugs, such as Belladonna, or Pneumonia will ensue.

The upper limbs may rarely lose power; numbness etc. however, is by no means common, and the patient is unable to pick up small objects such as lead pencils, etc. It is amazing how utterly helpless some of these cases may become and yet the heart remain free. Commonly the pulse markedly quick, suggesting some vagus involvement. But none the less I have seen nine cases of such severity as made them practically completely powerless and yet recovering has ultimately been complete. Formic Acid in large doses in normal saline per rectum proves invaluable. Thirty minims of the 25% solution, ⁱⁿ five or six ounces of saline, are given every four hours, and in those cases which react to the drug, the result is most gratifying. Recovery is slow, usually requiring up to 10 or 12 weeks from the onset.

A case of facial paralysis has not occurred in my series. Many writers, however, speak of its rare oc-

currence. Paralysis of the respiratory muscles is rare, and when it occurs is almost always fatal. The diaphragm or the intercostals may be separately involved, the former being the more common. Its occurrence must be watched for in the cases showing multiple neuritis.

Occasionally the Erector Spinae group of muscles are affected. The "wobbling" head of the patient when he is supported by the shoulders, is very characteristic. It is, however, a most rare occurrence.

Loss of the tendon reflexes is very common and very persistent when established. It is usually the earliest symptoms of paralysis and is generally the longest in duration.

Rolleston⁴⁷ has stated that Babinsky's sign is frequently elicitable in the acute stage of diphtheria, 19.6% of his series of 877 cases exhibiting the phenomenon. He attributes a certain prognostic value to it insofar that most of the cases which displayed it had complications later. It is, however, not pathognomonic of diphtheria, being observed in enteric, scarlatina, and pneumonia.

Post-diphtheritic paralysis, when not fatal is seldom permanent; and generally the worst cases recover in from 2 to 6 months or more.

Rest and strychnine have been mentioned as indicative in these lesions. Formic Acid, as before stated

is very valuable. It is recommended in doses of 5 to 20 minims of a 25% solution well diluted; and is generally well tolerated. I have, however, encountered patients unable to take it owing to the slight gastric irritation. Moreover, as stated before, in some cases it has seemed absolutely ineffectual, whilst in others its good effect has been prompt and lasting. It is said not to produce its therapeutic effect until 48 hours. I find that given per rectum, however, good results which I place to its credit are earlier apparent.

Massage is an advantage, where applicable. Electricity, however, seems to be useless as far as I have been able to discover.

(c) Toxaemia.

The treatment of this condition varies according to the extent of the chronic effects. In the marked cases, success is almost impossible of attainment. An odd case here and there may win through, but the majority die. The case of a relatively milder type have a proportionately better outlook. The intravenous injection of antitoxin, saline rectal injections, hypodermic indication, all are to be employed in trying to help the patient through this critical period. The outlook, however, is always grave, and a gloomy prognosis must be given and maintained, even in the cases which appear to react well to treatment. Only too

often one has seen parents and friends buoyed up with hope, at what appears to them, despite the advice to the contrary, to be definite improvement in a child's condition. These cases not rarely get over the first stage of the disease and for a week or so appear wonderfully better, and brighter, but unfortunately the second period of cardiac depression must be encountered, and the patient succumbs to cardiac paralysis.

A case illustrative of this is the following:

Eric C., aet. 14, admitted on the 5th day of disease with foetid membrane, involving the tonsils, fauces, and uvula, and a bacteriologically positive rhinorrhoea, suggesting post-nasal infection. 6000 units had been injected on the previous day, and 10000 units more injected on admission and again on the next. Under treatment the throat etc. cleared and the boy regained his spirits and appetite. On the 12th day an attack of vomiting ushered in the characteristic train of symptoms of cardiac paralysis and on the 14th day the patient died.

In those cases which show a tendency to haemorrhages from the mucous surfaces the prospect is also a bad one. During the past eighteen months, however, I have seen four cases showing moderate haemorrhage recover; and to some extent I am inclined to acknowledge the aid derived from the intramuscular injection of sterile gelatin. "Gelatina sterilisata pro injectione" is prepared by Messrs. Merck of Darmstadt and is put

up in ampullae of various sizes. I usually employ the 10 c.c. vial.

The bulb, after the neck has been broken off, is placed in warm water, until the gelatin is melted. Drawn out with an antitoxin syringe it is mixed with thrice its volume of normal saline, and the entire quantity injected deeply into the muscles of the buttock.

The action, in my opinion, is purely a mechanical one, rendering the blood somewhat more viscous and hence increasing its coagulability. Whatever may be its mode of action the effect is sometimes well defined in an hour or two. The bleeding diminishes and within 10 or 12 hours shows marked abatement; whilst in some cases it practically ceases within 24 hours.

If for no other reason than that of lightening the burden of the already well loaded patient this means at least decreasing the haemorrhage deserves employment.

(d) Laryngeal involvement.

The variability in degree of this type of diphtheria ranges from a simple laryngeal congestion, perhaps without actual formation of membrane, to an extensive deposit in the larynx, trachea, and bronchi extending occasionally along to the finest ramifications of the bronchioles; and danger from toxæmia is propor-

tional to the amount of extension. To the contrary, however, danger from actual suffocation may be urgent even in the relatively less marked cases. The condition may be an extension downwards of a lesion primarily affecting the tonsils, etc. or the nasal cavity. The symptoms are essentially those of laryngeal obstruction and are ingravescent in type, with the possibility of suddenly assuming a spasmodic element in their nature, and bringing the patient to a condition dangerously related to acute suffocation. The first signs of "croup" are usually seen in huskiness of the voice and the occurrence of a harsh "hard" cough of perhaps a high pitch in tone. Beyond these there may be no other objective signs. As the condition increases aphonia may be established, the cough more inclined to the brassy type, and some slight indrawing of the intercostal muscles.

On auscultation the breath sounds are found to be harsh and inspiration defective and prolonged. Accompaniments are not usually audible, being drowned by the harsh inspirations. Rise of temperature to 99° or 100° F. may or may not be present. The patient's colour and pulse meanwhile remains good. This phase however, is marked by the tendency to recurrent attacks of spasmodic dyspnoea. Perhaps without much warning, the child suddenly seems to meet with difficulty in breath-

ing. The face becomes congested, the eyes fixed, the alae nasi work visibly and the respiratory act is shorter and quicker. Inspiration becomes laboured and accompanied by a shrill stridor. The child tosses about at first but ultimately sits up to seek relief. A paroxysm of coughing commonly brings the patient almost to the verge of suffocation. The extraordinary muscles of respiration are called into action; the intercostals are drawn in whilst recession is marked in the supraclavicular^{and} epigastric regions. This fight in the earlier attacks, does not last long, a minute or two at most, as a rule, and the patient obtains ease by coughing up a varying amount of clear tenacious mucus. The child then lies down exhausted by the struggle, and perhaps sleeps. At progressively decreasing intervals, however, the attacks recur, each succeeding spasm being worse than the preceding one, until the dyspnoea is continuous and recession is seen with each respiration. By this time rest for the patient is impossible, and he tosses about in bed in his efforts to obtain relief. These two stages vary considerably in duration. I have seen cases brought to Hospital in this state after only two or three hours illness; whilst others may have been ill, with remissions, for as many days. The condition, in my view, is contributed to by at least three factors; the first is the simple preliminary

congestion of the larynx causing a narrowing in the "chink of the glottis". The membrane formation next adds to the process, whilst finally oedema of the parts increases the obstruction, and spasm of the glottis is superadded as the condition advances.

The child's condition at this phase is that of marked exhaustion and the effect of the impeded respiration upon the heart and circulation is manifested by the cyanosed face and rapidly failing pulse which, hitherto satisfactory, especially between the paroxysms, now becomes weak and quick and generally irregular. Failure of general strength ^{causes} ~~causes~~ the inspiratory efforts to be less forcible, and hence the recession is less pronounced and the respirations shallow and quick. And as the child is too weak to toss about, the restlessness diminishes. The strain upon the heart is shown by the change from cyanosis to lividity of the face and blueness of the lips. Perspiration gathers on the brow and nose and upper lip and the child gradually lapses into the final stages of suffocation. Should even a moderate degree of toxæmia be present the struggle is considerably curtailed in its earlier phases by reason of the inability of the heart to withstand the demands of the fight. The treatment of such cases is laid mainly in two directions:

(a) To relieve dyspnoea by removal of the obstruction by therapeutic means.

(b) Or failing this proceed to operative measures to prevent death from suffocation.

In the earliest stages, as a rule, antitoxin given freely will produce the desired effects. The child should be placed in a steam "tent" and the atmosphere kept moist by the use of bronchitis kettles, and a temperature of 65° F. maintained. Steam may thus be employed alone or with the addition of Tinct. Benzoin Co., Tinc. Iodi., ol Pini Pumilionis or Carbolic Acid. The iodine I have found valuable in stimulating mucous secretion of a fairly fluid nature. Benzoin acts as an anti-spasmodic. In the second stage, linseed meal jacket poultices frequently applied give relief in some cases, and I always employ them. The old-fashioned procedure of giving emetics is not to be recommended except in the milder cases, and only as an emergency measure.

Ipecacuanha Wine, the emetic most usually employed does not always produce vomiting and its depressant effect may constitute a ^{SOURCE} ~~source~~ of danger. Calomel, in fractional doses given frequently, has some supporters. I have tried this procedure but have not had marked results. Sublimation of calomel, to cause inhalation of this drug, has also been recommended.

The pulse and colour must be watched; failure of these demand early action on the part of the physician. If after a variable period the case shows no signs of

obtaining ~~ease~~, or of course, if the symptoms of dyspnoea increase in severity or if signs of cardiac embarrassment begin to appear, operative interference must be considered.

The two procedures employed are tracheotomy and intubation of the larynx, and the choice is usually decided by the experience of the medical attendant. The champions of Tracheotomy are loud in their praises of the operation and urge their claims on grounds of completeness, practicability and the like. Conversely, the supporters of intubation, are equally convinced of the greater desirability of their selection, the absence of "cutting" being included as a recommendation.

My experience has been almost entirely in connection with Tracheotomy. I have performed the other operation but, possibly owing to the lack of the tactus eruditus so to speak, I have not met with the results claimed by others. Intubation must of necessity be an operation for a Hospital or similar institution where ^{skilled} attendance is continuous. But for the general practitioner the prospect of an intubation tube being coughed out or otherwise losing its position, and no skilled attention promptly available, is by no means an alluring one. And despite the sentimental objections held out by some writers-"the fear of the surgeons knife"-one can hardly conceive of parents allowing this to stand in the way, of an operation, the aim of which is to save their child from a more or less ~~rapid~~ and

decidedly horrible death. A case of laryngeal diphtheria after tracheotomy might be left with some comparatively greater degree of mental ease than could a case of intubation. Even in extreme circumstances, a plugged tracheotomy tube could be taken out and an extemporised dilat~~ion~~ held in the tracheal wound until other assistance is obtained; but what could be done should an intubation tube be expelled? The occasional "rolling up" of the membrane before the intubation tube as it is being introduced, may constitute an addition to the danger. And again, the postulate that the apparatus for immediate tracheotomy ~~is~~ to be readily available lest the intubation be unsuccessful reveals a by no means inviting aspect of the case. A successful intubation is indeed a less awesome picture than a successful, ^{though} perhaps sanguinary tracheotomy. Nevertheless, my personal case inclines me to the latter. The rush of air from the trachea when it is incised, frequently carries out with it a good quantity of membrane and should any partly loosened pieces be visible through the wound these also may be detached; and consequently the patient may be additionally helped.

The resulting cicatrix after tracheotomy, also held by some to be an objection, is not of necessity a large one. The primary incision is only an inch or so, and in those cases which I have had the opportunity of examining a year or more after their operation the scar

has been almost unnoticeable. One or more of the danger signals having been observed it is decided to operate. I do not propose to detail the operation step by step, but shall only refer to some salient points.

The operation may be postponed later in Hospital than in general practice, because of the constant proximity of skilled assistance. ~~and~~ I have not found a general anaesthetic to be essential and in fact, it is, in my opinion, undesirable, owing to the grave condition of the child. On rare occasions I induce local anaesthesia with the Ethyl Chloride spray; this is in order to eliminate the pain of the incision, the only actually painful step in the operation.

It is unnecessary to insist upon a thorough antiseptic cleansing of the site of election. I invariably perform the "low" operation; better results have been derived from this than from the "high" operation in regard to the removal of the tube - the result no doubt of the avoidance of the possibility of injuring the cricoid cartilage. Bearing in mind Professor Chiemes axiom "keep to the middle line", an incision of one inch or even less, in length is made, the lower end of which reaches about half an inch above the suprasternal notch. The knife is then laid down and the rest of the dissection is made with a blunt dissector. I have found that a "director" acts admirably for this purpose; and hence practically all bleeding is elimin-

ated. The trachea bared, it is held by a sharp hook, and incised; I find that it is a good rule to make this incision as large as possible. Forceps or dilators are then introduced and the patient allowed to "blow" for a few moments; this relieves the heart, and often allows of the ejection of much membrane. Absence of this rush of air denotes either that the trachea has not been entered or that the child is "in extremis" and requires prompt artificial respiration.

The tube - of not too small a size in young children - is introduced. "No. 22" in Parker's type is of a good every day size. The entire operation should not require more than four or five minutes. The patient is then put back to bed. The steam, my experience leads me to believe, should be continued after the operation-the-patient-usually-sleeps tube has been removed. Directly after the operation the patient usually sleeps, and the child should not be disturbed save only for the most exceptional reasons.

It is presumed that serum has been given already. If for any reason, such is not the case, the earliest opportunity should be taken for its administration. The tube, provided serum has been freely injected, may as a rule be entirely dispensed with at the end of 36 hours.

Circumstances militating against the removal of

the tube are: Extensive involvement of the lower expiratory passages with membrane, and the consequent "shedding" of pieces of membrane of varying sizes; pneumonia and broncho-pneumonia; and a highly strung and nervous disposition of the patient. All except the last may derive improvement from further injection of antitoxin. For the last, the exhibition of small doses of Ammon. Bromid. or Veronal generally forms an aid to successful removal.

In association with the high operation, another condition may arise. Injury to the cricoid cartilage is commonly the cause of this trouble and is an exceedingly intractable complication.

In my series, I have had 152 opportunities of performing tracheotomy, of which 120 have been of the "low" type; and in these latter excluding of course those cases which have died early, on only two occasions has difficulty been experienced in removal of the tube for reasons other than extensive infection, broncho-pneumonia or other organic complication. The two cases mentioned were, it is presumed, due to the highly excitable temperament of the patient.

From the high operation the results obtained were most discouraging in regard to tube removal.

Nearly half of the cases gave trouble in this regard and of the cases which after repeated attempts dispensed with the cannula, all but five developed a peculiar inspiratory stridor within a week or so, which increasing

day by day, ultimately caused death from syncopal-asphyxia. Whether this was the result of injury to the cricoid cartilage or of cicatricial contraction I do not feel disposed to argue.

Re-tracheotomy at a lower level was tried in one instance but the patient died. I am inclined from my own observations and that of others more experienced than myself, to suggest Intubation of the Larynx coincidentally with the attempt at removal of the tracheotomy tube if the cannula is not dispensed with at the end of ten days. The commonest complication - broncho-pneumonia, will be discussed later.

In reference to after treatment, a point relating to feeding may be mentioned. Some writers insist on the necessity of nasal feeding for these cases, My experience has not led me in this direction at all, and I have ^{found} that a careful nurse is able to feed a patient satisfactorily and with comfort to the latter, by means of the ordinary feeder, or feeding cup. Nasal feeding in diphtheria has never commended itself to me. The resentment displayed by some children, even to the most careful and gently persuasive approach and method, is so alarming that I am content to appeal to the rectum when the oral mode is for any reason unavailable.

In the absence of pulmonary complications the case

may generally speaking, be treated on the same lines as laid down at the beginning of this section.

Treatment of other complications.

Broncho-Pneumonia.

This condition is most usually seen in Diphtheria as a sequel to Tracheotomy, in cases in which the membranous formation reaches down to the finer bronchioles. It is a complication of grave significance, partly as a result of the enormous area for the absorption of toxin involved, and partly by reason of the pneumonic condition handicapping the respiratory interchange of oxygen etc., and partly by reason of the strain thrown upon the heart.

As to treatment, I have found oxygen inhalations of advantage. Jacket poultices of linseed too have been valuable. Burney Yeo's suggestion of the utilisation of Quinine in an effervescent mixture⁴⁸ is of decided advantage in these cases. Two mixtures are made thus: No. 1, contains the Quinine Sulphate dissolved in Citric Acid; No. 2, contains Potassium Bicarbonate as the essential alkali, and to this solution such drugs as Ammon. Carbonate, Potassium Iodide, Strophanthus Tincture, Tincture of Nux Vomica etc., may be added as required. I have invariably utilised this combination and have had every reason for satisfaction with the results obtained.

Antitoxin I have found has a very beneficial ef-

fect upon these cases, and consequently should be given freely. I have tried Anti-Pneumococcic Vaccine, but with indifferent results.

Adenitis.

Linseed poultices are of value in relieving pain and inflammation. Should the glands break down, early incision is indicated. The pus in some cases, is of a peculiarly sour smelling order.

Otitis and Otorrhoea.

These are relatively uncommon, and the Otitis, unlike the scarlatinal variety is not frequently associated with pain, When present, however, the pain may be allayed by the application of linseed poultices.

The ear discharge may in some cases show the presence of the bacillus diphtheriae, but more commonly it displays only the Pyogenic Cocci. Cleanliness should be maintained by careful douching with Lotic Carbonis Deterg (vel Picis Carb.) and after, the use of "drops" composed of equal parts of a 1% solution of Perchloride of Mercury, Absolute Alcohol and Liq. Hydrogen Peroxid. (20 vols).

Albuminuria.

Two types are seen: The first is present in the early stages, i.e. the first week. Older writers speak of its presence as common. My experience leads me however, to a divergent belief, except as regards

those cases which are toxic on arrival. Only 2% of the ordinary cases display albuminuria on admission, and in these it has usually been of the "febrile" type.

The second form usually appears in the second week and onwards, and is present as a rule only in severe cases and fairly severe cases.

It may, generally speaking, however, be construed as a sign of severity.

Restriction of diet has no apparent effect, adverse or otherwise, and as a routine, I make no alteration in regard to the patient's food. Similarly drugs appear to exert no influence upon the condition.

Jaundice.

On three occasions the symptom of jaundice has occurred in my series of cases. In only one of three patients was the primary manifestation of diphtheria severe. The icteric discolouration of the skin and conjunctivae was moderately well defined in this latter case and one of the others. In all the urine and stools were characteristic; and the liver only very slightly enlarged. No case displayed itching of the skin. All the cases developed the condition in the 3rd week, and the duration varied from 8 to 11 days. The condition was presumed to be of haematogenous origin, the consequence of the absorption of the toxins.

Maintenance of free intestinal action was the line of treatment pursued. All the cases ultimately recovered.

IV. Technique of Serum therapy with discussion of Anaphylaxis.

Modes of administration of antitoxin.

Serum may be given subcutaneously, intramuscularly, intravenously, per os, ^{or} per rectum. Each method has its advantages and disadvantages, real and alleged, and each has its champions and opponents amongst clinicians.

For the Hospital or special Institution with its resident physician the troubles and dangers entailed in the hypodermic and intravenous methods are relatively slight, but if considered from the point of view of the physician engaged in a busy general practice, these appear very large when balanced against the simplicity of the oral or rectal modes of exhibition.

I. Subcutaneous Method.

None the less ^{the} subcutaneous or hypodermic method has been, and still is the orthodox means of administration. The details of preparation of the part where it is proposed to perform the injection one need not enumerate; nor is it necessary to do more than mention that the serum syringe, needle, hands, and site of injection be as near aseptic as is possible.

Site: The area of the body in which the injection is to be made is usually dependent on the looseness of

the skin and underlying tissues. Some prefer this part and some demand that. The common sites are the abdominal wall, the flanks, the area between the scapulae, and the buttocks.

It has generally been my experience to utilise the abdominal wall, over the iliac fossae for the purpose. The advantages of this situation are: the patient is able to lie with a fair amount of comfort, and may move himself without a lot of pain; the puncture is easily exposed for any subsequent examination which may be necessary; and should septic changes unfortunately arise, the focus is in a convenient position for the requisite attentions. In this position I have been able on many occasions to inject 20 or more c.c. by disconnecting and refilling the syringe, leaving the needle in situ and so necessitating only the one puncture for 8000 or even 10000 units of standard antitoxin.

For this method the advantages claimed are: Rapidity of action: The serum injected under the skin must necessarily be absorbed more rapidly than when introduced via the stomach or the rectum. Though obviously it is not so rapid as when introduced directly into the blood stream by the intravenous method.

My experience has in the main been of this method, and as a rule I would estimate that the effects of

antitoxin action may be expected to be first observed in about 8 hours or thereabouts after injection. Henderson Smith's⁴² computation that the serum injected thus is not absorbed until the expiration of 48 hours, may be in essence correct; all the serum may not be actually at work in the circulation, but some certainly must be.

Approximate certainty of dosage: when given by mouth or by rectum the act of vomiting or evacuation of intestinal contents may result in the rejection of of the serum.

Given with proper care and certain precautions such accidents might possibly be obviated.

Risk of air embolism.

This may be eliminated altogether if a site free from veins be selected, and the syringe contain no air bubbles. The disadvantages alleged comprise: Pain of the injection: This can be reduced to a minimum by the use of an Ethyl Chloride spray to overcome the pain of the puncture. The actual injection is not painful if the serum be introduced slowly and gradually. Up to 8000 units of standard serum, 20 c.c. in volume, may be given if introduced slowly and carefully with practically no pain to the patient even in the case of young children.

Serum Abscess. Always is the result of bad technique, and easily avoided by strict aseptic or antiseptic methods. Three years ago, however, a number of serum abscesses occurred within a few days in patients under my charge. The technique of the ministration, as far as one could find, was sufficiently above suspicion. The cases were not "septic" in any way, nor was the ward. A bacteriological examination of some of the unused vials of serum - delivered to me only a few days previously by a firm which shall remain nameless - showed the presence of pyogenic cocci. The incident is mentioned solely on account of the interest bred of its rarity.

Serum Sequelae: i.e. Serum rash and Sickness, and Anaphylaxis. These concomitants of serum exhibition, when in their more severe and serious forms constitute the gravest indictment against the hypodermic administration. Happily anaphylaxis is rare, and fatal anaphylaxis still rarer, yet the possibility of such tragic complications must not be lost sight of. Simple serum rash is not at all a serious or weighty factor and when compared with the danger of diphtheria is still more trivial. Serum sickness is more to be considered, though again by the same comparison, it too diminishes in import. This topic will be discussed more

fully in a later section.

A modification of the subcutaneous method is that of intramuscular injection, usually in the buttocks or thigh. I have found no advantage in this, over the subcutaneous method proper.

II. The Intravenous method.

Employed in the same manner as intransfusion into a vein, or the needle of the syringe may be plunged directly into a vein previously enlarged by compression of the part above. The Median Basilic vein is usually selected, as being the most convenient.

This method was first suggested by Cairns⁴³ and later was supported by other observers including Emery⁴⁴, Bullock⁴⁵, Roehr⁴⁶, the last named recommending the suspension of the serum in 20 to 30 ounces of normal saline.

Henderson Smith⁴² speaks highly of the prompt and beneficial reaction which he has obtained in almost hopelessly toxæmic patients coming late under treatment. Gratifying and encouraging as these reports are, yet the danger of fatal complications arising during the act of injection owing to the introduction of an air bubble into the blood stream, render one timorous of the undertaking. And moreover, it is by no means a simple or easy action to plunge a serum ^{needle} accurately into a vein of the arm of a child, particularly if the patient should have an arm well clothed in fat. Nevertheless the almost miraculous results obtained in presumably

well-nigh hopeless cases, by reputable observers, fully justify the method. I have employed the method, but the occasions have been so few as not to justify a definite statement on my part.

III. The Oral Method.

There exists a great deal of divergences of opinion regarding the propriety and therapeutic utility of administering antidiphtheritic serum per os, some clinicians reporting excellent results, whilst others consider the practice by no means worthy of recommendation. Personally, I have had most satisfactory results from this mode of exhibition. It is invariably my rule to give serum, when used as a prophylactic, by mouth. On two occasions when a case of diphtheria has occurred in my Scarlet Fever Wards (26 patients) I have given contacts prophylactic serum orally, and in neither incident did any further case of diphtheria appear. Similarly, in general practice, on the occurrence of a case of diphtheria in a house the other occupants have been successfully protected, in many instances. The most marked of such cases was that of a child æt. 6 years, who was discovered suffering from extensive diphtheria, membrane formation, involving the tonsils, fauces, soft palate, nasal cavities, and pharynx, obviously a case of many days duration. There were four other children in the family, three younger than the

patient, and the parents. All were given prophylactic serum per os, and the patient was removed forthwith to Hospital; and none of the other members developed the disease.

I usually administer for prophylaxis, 2000 units suspended in about 2 or 3 ounces of normal saline solution, when the stomach is empty. Food is refrained from for $1\frac{1}{2}$ to 2 hours. Or it may be given in milk, following the lead of Ehrlich who produced immunity in young guinea pigs by feeding them on milk containing antitoxin. McClintosh and King⁴⁹ suggest that a small amount of Sodium Bicarbonate be given in the solution with 4 or 5 drops of extract opii and 4 to 10 drops of a saturated solution of Salol in Chloroform, half an ounce prior to the serum, to overcome any deteriorating or nullifying effects which the gastric secretions, or digestive processes may exert upon the serum. They further recommend abstension from food for four hours.

Attention to the oral administration of serum has of recent years been particularly drawn, by reason of the sudden and dangerous, and at times fatal phenomena attendant upon its injection. (~~See~~ serum sequelae, anaphylaxis etc.) Goodall⁵⁰ recently denounced the hypodermic administration for purposes of prophylaxis as "not only unnecessary but unjustifiable" by reason of anaphylactic possibilities. Out of over 250 patients

to whom I have given Antidiphtheritic Serum by mouth, I have only encountered Serum Rash (Urticarial in both cases) on two occasions; in neither case was a previous history of previous occurrence of dietary, etc., nettle-rash elicitable, and consequently I am forced to the conclusion that they were cases of true Serum Rash. I have given antistreptococcic serum orally and per rectum to over 500 patients suffering from the more severe forms of scarlet fever and have seen no rashes etc. resulting.

The taste of the serum cannot be described as a disagreeable one; in fact, most people discern a resemblance to gravy. The distaste, of a sentimental order against "drinking horses blood" occurs only in those conversant with the manufacture of the article.

Again the objection of some individuals to the "operation" of hypodermic injection or the abnormal fear of the pain, may be insurmountable obstacles to subcutaneous administration.

As a curative measure oral exhibition is by no means valueless. In fact, where there is a history of any attacks of asthma or kindred complaints, some clinicians demand this mode as being the only legitimate method, unless the risk of anaphylaxis be ignored. On numerous occasions I have treated cases of definite

and bacteriologically proved diphtheria by oral serum, and in no case over the age of 16 years have I had cause either in the early or later stages for dissatisfaction. Twelve months ago the experimental use of serum by mouth for curative purposes was commenced in our Wards. Only patients of the age of 16 years and over, and of mild degree, were thus treated. Entirely satisfactory results were obtained.

Emboldened by this, we extended the age limit to 10 years and upwards. Twenty mild cases between 10 years and 16 years were so treated. All the throats "cleared up" in a desirable manner; but one case, a boy, aet. 10, at the end of the second week redeveloped a sore throat upon which at the end of 16 hours membrane appeared. Cultivation displayed a pure growth of the bacillus diphtheriae. Serum was then given to the patient hypodermically and the case ultimately attained a successful issue without any paralytic or other complication. It is still our practice to give serum to all adult patients, except in very severe attacks, by the mouth and treat them in the ward along with other cases of diphtheria; and on no occasion have untoward symptoms by way either of relapse or complication, been met. Children of tender years have not been so experimented with by us, owing to their smaller general powers of resistance and greater susceptibility to the

Klebs-Loeffler Bacillus and its toxins. Yet I have no doubt that mild cases seen early could be treated with antitoxin per os quite successfully. Hall⁵¹ recently contributed an example of a young child with incipient diphtheritic "croup" satisfactorily relieved by serum given by mouth.

Another mode of employing the oral method of which I frequently make use, is as an augmentation to the hypodermic injection. The following illustrative case is in its final stage of convalescence at the moment of writing. Nurse L., on duty in diphtheria ward; came under observation on 3rd day of disease; firm patch on each tonsil, bacteriologically positive; 8000 units antitoxin injected, throat syringed with Lysol solution (~~2~~^{3/4} ~~grains~~ ^{ad} OI) four hourly; only slight improvement at end of 24 hours; further 8000 units injected. Throat not cleaning satisfactorily at end of second 24 hours. Ordered 2000 units per os in ³3I normal saline every four hours. After second dose more definite effects noticed. Membrane thinning and separating. Throat clean after 8 oral doses, i.e. after 32 hours oral serum.

The exact effect of the serum per os after primary Hypodermic Injection, I am unable to satisfactorily explain. Whether the actual contact of the serum with

the tonsils in the act of swallowing, produces a benefit or not, I cannot state. Five years ago Paton⁵² spoke of this "combined method" very encouragingly and later⁵³ expressed the opinion, helped by the results of experiments, that the serum repeatedly administered by mouth maintains tissue, tone and resistance. I am led by my experience of this method of the combination of primary injection and secondary oral dosage to have great faith in the procedure; and it is my routine method in the wards when dealing with the more obstinate cases. As a general practice 2 injections are made; in exceptionally severe cases 3 may be given. Thereafter oral serum in repeated four hourly doses of 2000 units each, is ordered, and, in most cases 12 such doses are sufficient, combined, of course, with systematic syringing etc., procedures dealt with under the heading Local Treatment.

IV. The Rectal Method.

As long ago as 1897 Chantemesse⁵⁴ experimented with antidiphtheritic serum given per rectum and obtained satisfactory results. Parkinson⁵⁵ more recently has spoken with approbation of the procedure.

My experience of this mode has been limited in regard to diphtheria, to comparatively few cases and hence by reason of paucity of opportunities for obser-

vation I cannot testify in any definite direction. Frequently, in cases of Septic Scarlet Fever, have I given antistreptococcic serum viâ the bowel and have always been satisfied. Those cases of diphtheria which I have treated by this means with Antidiphtheria Serum have been exceedingly slight.

The usually employed procedure has been to empty the rectum with plain warm water, and then to slowly inject the serum diluted with about 4 or 5 ounces of normal saline solution high up into the bowel by means of a soft red rubber catheter continued externally in a soft tube terminating in the usual funnel apparatus, or in place of the funnel the external or barrel portion of a male glass syringe 2 ounce size. Many of the advantages of the oral method are shared by this modification.

Clinical Effects of the Hypodermic Administration of Antitoxin.

The tumour caused by the subcutaneous injection as a rule disappears in half an hour or so, leaving no trace behind save the minute needle puncture. Not rarely, however, a certain amount of local redness remains for some hours and sometimes for a day or two; this area may itch very considerably. On much rarer occasions a raised dull erysipelatoid condition of the

skin may be seen, accompanied by a rise of temperature and some general malaise. I am inclined to the opinion that these latter may in some way be related to the anaphylactic conditions mentioned elsewhere. They usually subside under palliative symptomatic treatment.

General Effects are mainly dependent on the earliness or otherwise of the institution of serum treatment. In simple cases there is usually a rise of temperature within an hour or two accompanied by the quickening of the pulse rate; this usually persists even after the temperature has fallen. The temperature generally returns to normal or subnormal in 48 hours or so if the case is one of pure diphtheria. If, however, the infection is a mixed one and cocci are causing some part of the lesions, then the fall of temperature is considerably delayed; similarly broncho-pneumonia as in laryngeal cases, adenitis, etc., may also delay the fall. Mention may be made here of certain other general symptoms which are seen only in rare instances. I have met with a number of cases in which sweating - sometimes profuse - has occurred within a few hours. On rare occasions also the patient may be subjected to repeated attacks of sneezing; and certainly in some laryngeal cases, the croup and dyspnoea, become transiently more pronounced a few hours after injection. Then there are the unfortunate cases in which death,

preceded by a short sharp attack of dyspnoea and pseudo-asthmatic symptoms, has taken place. Individual peculiarity and susceptibility to certain unknown elements contained in the serum are, I am inclined to believe, the sources from which these trains of symptoms take their origin.

Effect upon the Membrane.

This is best observed in the simple cases of Tonsillar Diphtheria. As a rule, in about 10 hours or so the first sign of the action of the antitoxin is to be noticed. It is observed as an inhibition of the spread of the membrane. Later, the edges of the patch are seen to become slightly "puffy" and detached from the underlying tissues, and may appear slightly turned, or rolled up. This separation continues and the membrane may "per se" be cast off in its entirety or piecemeal, or the mechanical effect of the syringing of the throat may help to release it, in the course of 48 hours or so. Slight haemorrhage may accompany the detachment. As a rule it is not serious, either in urgency or in import. Such prompt effect is only seen, however, in simple cases coming under treatment early, in those in which the toxæmia is established or profound, little or no effect upon the general condition is seen. The separating membrane may be accompanied by much uncontrollable oozing of blood, or in marked

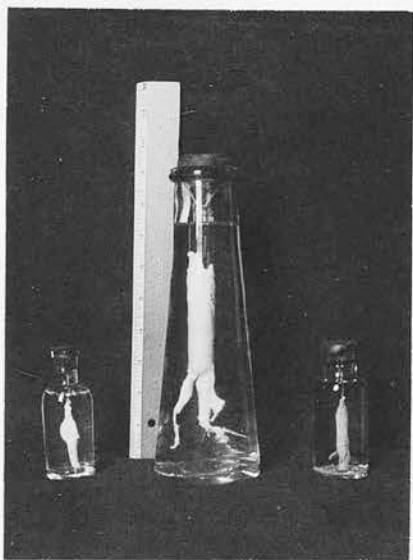
cases by urgent haemorrhage. In very favourable cases the throat should be clean in 24 or 48 hours. If no change has taken place within 24 hours then the question of administering more serum must be considered. The "solvent" effect of the serum is more apparent upon the tonsillar lesions than in other pharyngeal situations. If the membrane has not entirely disappeared from the tonsils, etc. by the fifth day after the commencement of serum exhibition, the prognosis of the case is not at all favourable.

In Nasal Cases as a rule the first serum effect is seen as a diminution in the amount of nasal discharge, and as changed to turbidity from comparative clearness in its appearance. Stringy shreds of membrane are seen to be shed and the nasal mucosa appears to lose much of its swollen appearance. With 48 hours nasal respiration is reinstituted and ⁱⁿ the crusts of dried secretion are seen to be forming. The excoriation of the nostrils and adjacent lip heals, and in about 4 days, the nose, except for a somewhat persistent redness of the mucous membrane, approaches the normal. Such are the phenomena observed in favourable cases.

Laryngeal Diphtheria. It has been mentioned just previously that in some instances the symptoms of dyspnoea are rendered temporarily and transiently more

urgent after injection of serum. This may be simply mechanical in causation, the throwing into the circulation of a more or less comparatively large amount of fluid - ordinary grade antitoxin averages 400 units in 1 c.c. - say 10000 units resulting in an absolute increase in blood tension and consequently an overplus of congestion and swelling of the mucous membrane of the lungs and elsewhere; or it may be one of the phenomena included in the anaphylactic condition. Speaking generally, however, in simple cases of early Laryngeal Diphtheria, the beneficial effects of the serum may be looked for in about 8 hours. The respiration shows less urgency and the intercostal and epigastric indrawing appearing somewhat diminished, particularly if the child be sleeping. The cough commences to show signs of "softening" and phonation becomes less embarrassed, in 24 hours or more.

If tracheotomy has been performed the membrane loosened from the lower respiratory tract early commences to be expelled from the tube, sometimes as small shreds in the mucous discharge and sometimes as definite casts of the trachea, or trachea and bronchi. The tube may easily be removed, I have found from experience, in 36 hours or so, and in many favourable cases respiration "per vias naturales" begins within 48 hours. A common cause of trouble in taking the tube out and ob-



taining the natural mode of respiration lies in the exhibition of too small an amount of antitoxin.

In cases where tracheotomy has not been necessary the return to normal is more gradual, within 3 days or so, beyond a slight croupiness of the cough or huskiness of the voice when labouring under excitement or emotion as in crying, etc. the child appears normal.

The accompanying photograph is taken of a case expelled as follows:-

Florrie G. aet. 16 years admitted to Hospital on the 5th day of disease, with a fairly small patch on one tonsil. Respiration did not appear to be sufficiently embarrassed to require tracheotomy. 8000 units of antitoxin were injected. The throat began to clean up satisfactorily. During the third night after admission patient was suddenly seized with a violent fit of coughing, associated with a choking sensation. The nurse in charge examined her throat and observed something like partly detached membrane; of this she seized hold with forceps and after some time extracted the cast entire.

The patient, contrary to expectations, passed an uneventful convalescence and had no paralysis.

The two smaller specimens are tracheal casts, coughed up during life via the ^{tracheal} ~~facial~~ incision, in cases of tracheotomy. Concurrently with the "cleaning up"

of the throat etc., the adenitis subsides, the result of the diminution of local absorption of toxins. The clinical effects which have just been described are subject to many modifications and in all cases refer to simple uncomplicated cases in which antitoxin has been administered early. The various elements militating against the anticipated beneficial effects of the serum, have been dealt with elsewhere in this treatise.

Serum Sequelae:

The phenomena resultant upon the injection of serum, form at the moment, one of the most interesting of the many problems of immunity. For the beneficent effects of serum therapy we have every reason to be grateful, but for certain other results of serum injection, feelings of a different order can only be expressed.

The clinical effects of antitoxin upon diphtheritic lesions have already been discussed in the preceding chapter and incidentally the early complications which may arise therefrom.

The sequelae to be discussed in this section comprise, Serum Rash, "Serum Sickness", and Anaphylaxis.

Anaphylaxis or Hypersusceptibility.

The occurrence of an urticarial eruption sometimes accompanied by pains in the joints, after the

injection of the then "new" antitoxin, was early noted by Lublinski,⁵⁶ and Scholtz⁵⁷ in 1894, and attracted much attention.

Johannesen, in the following year, experimenting with normal horse serum, found that injection of the serum of non-immunised horses produced the same phenomena, a result which suggested that the sequelae were not due to the antitoxic elements of the antitoxin.

In 1896, Hartung⁵⁸ collected statistics of a number of cases, and from his observations argued that something in the individuality of the horse itself was the causal agent.

The succeeding years were rich in experimental and clinical contributions to the subject; and in 1905, Von Pirquet and Schick published "Die Serumkrankheit", a book embodying their own work and that of other observers, and bringing the subject completely up-to-date.

It is found that, speaking generally, the injection of serum and the appearance of the rash are separated by a variable period of time, most usually of from seven to fourteen days, though these limits are not definite. This period, it is suggested by Von Pirquet and Schick constitutes the Incubation Period, and in 20% of their cases varied between eight and twelve days.

The simple rash coming on in this time, and obtainable by the use of normal horse serum, was termed the "Normal reaction". The normal reaction may also be produced by the serum of other animals but to a less marked extent. Certain circumstances, some of known nature and others inexplicable, had however, the effect of producing much more severe symptoms, i.e. an "abnormal reaction"; and this condition of hypersusceptibility might be displayed under two different conditions,, viz.

1. Those in which there had been a previous injection of serum, and

2. those in which there had been no previous injection.

The first subdivision is further divisible into three classes, according to the clinical manifestations of each group:-

(a) Excessively profuse and persistent rash with severe concomitant symptoms such as fever, post sternal and epigastric pains, congestion of mucous membranes etc. but all occurring after the usual period of incubation;

(b) Similarly severe symptoms, but appearing earlier than the usual incubation period, i.e. an "accelerated reaction"; and

(c) in which the symptoms arise within a few minutes or a few hours after the injection, i.e. there is

an "immediate reaction". This last class shows symptoms of an especially severe nature, and includes rigors, cyanosis, and collapse, as well as profuse urticaria etc. and may bring the patient to a state of grave danger. The second division comprises those cases in which there has been no previous injection. The phenomena are different and are characterised by appearing practically at once or within a few minutes, and consist of urgent dyspnoea, rigors, cardiac distress, and not uncommonly, death.

To recapitulate briefly in tabular form we have:

I. Normal Reaction: with incubation period of 8-12 days and mild symptoms.

II. Abnormal Reaction.

A. With previous injection at a period not less than the normal incubation period before the second. 3 clinical types:

1. Normal incubation period, with severe symptoms.
2. Incubation period shortened to a few days with severe symptoms. "Accelerated Reaction."
3. Severe and sometimes dangerous symptoms appearing in the space of ~~a~~ a few minutes or hours. "Immediate reaction".

B. Without previous injection.

Symptoms arising in a few minutes, displaying urgent respiratory and cardiac distress, causing rapid death in a good proportion of cases attacked.

Gillette⁷⁰ has collected 30 cases of this type and of these 15 died. He quotes the following case:

An asthmatic man, aet. 52, was being given 2000 units of antidiphtheria serum with a view to curing his asthma. Within a few minutes of the injection he complained of a prick¹ing of his neck and chest; he then said he could not breathe and indeed stopped breathing. He died in tonic spasm within ten minutes of the commencement of the injection. Nothing was revealed at the autopsy.

Of these 30 cases, 22 showed a history of previous asthmatic or similar attacks.

A similarly fatal case was reported in the Daily Chronicle, Nov. 29th, 1908, that of a young woman in Oxfordshire who died practically immediately after a prophylactic injection of serum.

It is thus seen from the foregoing that the injection of serum, whether primary or secondary, may result in the production of symptoms in certain human beings and animals, of an alarming and at times fatal nature, and due to a state of unduly high susceptibility to some substance either contained in the serum or formed in the body as a result of the presence of the serum in

the blood.

Regarding the first group (A) of "abnormal" reactions it has been laid down as a postulate by Von Pirquet and Schick that the second or later injection must be made after a period had expired which was as long as or longer than the "normal" incubation period of seven days or thereabouts. The period may be longer, but never shorter.

The same observers, by experiment obtained an "abnormal" reaction after a lapse of three years after the primary injection.

Currie⁶² obtained a slight "immediate" reaction after a period of ten days; this is the minimum period on record for this particular class, whilst the longest recorded period is three years, noted by Von Pirquet and Schick.

The term anaphylaxis (Greek, against protection) was applied to this state of excessive susceptibility, by Richet who experimented originally with actinia poison in dogs.

The condition is also known as "supersensitive-ness" or "hypersusceptibility", and may be brought about by the introduction into the body of certain protein substances, such as blood-serum, egg-white, milk, and also bacterial proteins and vegetable albumins. Attention was first drawn to the reaction by Otto,⁶⁰ fol-

lowing observations and suggestions made by Theobald Smith. The reaction was also observed independently by Rosenau and Anderson.⁶¹

The "Serum Disease" which sometimes follows the injection of antitoxic horse serum belongs to the same group of phenomena. The toxic action following the injection of the serum in man, is due to a protein in the horse serum, and is entirely independent of the antitoxic properties of the serum.

The tuberculin and mallein reactions are other well known instances of anaphylaxis. A definite period must always elapse between the first and second injection in order that the toxic effect may be manifested. In the sensitization of guinea-pigs against horse serum, this period, as a rule, is from ten to twelve days. The toxic action of the horse serum upon guinea pigs has been studied with especial fullness. Sensitization may be effected by very small quantities; Rosenau and Anderson have reported that in one instance 1/1,000,000 c.c. of horse serum was enough to render a guinea pig susceptible. Larger doses, usually from 3 to 6 c.c. must be given in the second injection in order to produce a fatal result, but so small a quantity as 1/10 c.c. may sometimes suffice to produce serious symptoms. The liability to react hypersensitively is transmitted from mother to offspring, the young of ac-

tively sensitized female guinea pigs being themselves hypersensitive. The male does not transmit this quality. The anaphylactic reaction depends upon the development of a special antibody; passive hypersensitiveness may be induced by transfer of serum from a sensitized animal to a normal one. Many theories and explanations have been put forward as to the nature and cause of these phenomena, but up to the present conclusive evidence of a real comprehension of the condition is not forth-coming.

That hypersusceptibility might be produced by a second injection was first demonstrated by Arthus.⁶³

The original theory that the condition was actually due to the formation of precipitins, was discarded by Von Pirquet and Schick, who considered it the result of a reaction between the horse serum and some antibody "allied to the precipitins", the incubation period being made up of the time required for the elaboration of the antibodies. The abnormal reactions were, they considered, due to the presence of a variable amount of antibody free in the blood so caused by the primary injection, meeting with the serum of a further injection, made after the expiration of the suitable period, and resulting in the alteration of the incubation period etc. These writers also applied the name "Allergie" to the condition, signifying the alter-

ed power of an organism to react to a foreign protein. The term "anaphylaxis", originally applied as an anti-thesis to prophylaxis, they considered in some sense a misnomer, since anaphylaxis may be of some value to the organism as a protection. During the last five years the subject has assumed a large importance and an enormous amount of experimental work has been directed towards the discovery of the real nature of the condition. It is therefore obvious that in a limited article such as this, one is unable to review and discuss each series of results and every theory advanced.

A recent contribution to the subject by Anderson and Frost⁶⁴ is very valuable. Using horse serum and white of egg as "antigens" they studied the anaphylactic antibody particularly, and gave it the name "allergen". They believe that hypersusceptibility to a foreign protein consists in an increase in the normal power of assimilating this protein, particularly an increase in the rapidity of the reaction. Anaphylactic shock, in their opinion, "is a disturbance of metabolic equilibrium", rather than the effect of a specific toxic action; and further, they consider that anaphylaxis is followed by a state of "anti-anaphylaxis" in which the animal is in a condition of immunity to anaphylactic shock from a further injection of the same antigen. This anti-anaphylaxis is a temporary condition which passes gradually into a condition of relative insuscep-

tibility, which is distinguished as "immunity" proper. They conceive anaphylaxis as a step towards immunity, which is an increased capacity for safely and rapidly eliminating the specific antigen protein. Billard⁶⁵ recently published an article in which he classifies urticaria, hay-fever, asthma, and the idiosyncrasy possessed by some people towards certain articles of diet, as all being manifestations of anaphylaxis; he sums up his view thus: "I am able to conclude that neuroarthritics and especially asthmatics and those predisposed to hay-fever, are persons victims to anaphylaxis either hereditary or acquired."

Miller and Root⁶⁶ suggest that some relation exists between the anaphylactic condition and "status lymphaticus". As a sequence to this suggestion some clinical experiments were prosecuted by myself and published in a note as follows⁷⁷.

"The effect of the administration of thyroid gland substance upon serum rash and serum sickness and diphtheria".

" The occurrence of serum rashes, either alone or in conjunction with high temperature, arthritic pains, oedema, inflamed throat, adenitis, rhinitis, albuminuria, forming the syndrome designated by Von Pirquet as "serum disease", after the hypodermic injection of diphtheria antitoxin and other sera, and the graver anaphy-

"lactic complications, have attracted very considerable attention during recent years, both at home and abroad.

The conclusions most generally accepted are:

1. That the phenomena are not due to any substance in the antitoxic elements of the serum, but to a protein body inherent in the serum itself.

2. That serum rash and serum sickness or disease may follow one injection only, but will follow more rapidly when a second injection is made, coming on earlier as a rule, the more recent the first injection; and

3. That anaphylaxis usually only becomes a possibility when a second injection is made from ten to twelve days and onwards, after the primary one.

The simple serum rash may be of no consequence in a case of diphtheria, insofar as bad results are concerned. On not a few occasions however, I have seen infants rendered distinctly "croupy" by oedema of portions of the air passages, coincident with, or resultant upon, an urticarial serum rash. Serum sickness, where severe, may very considerably tax the patient whose system is already burdened with the toxins of diphtheria; and I cannot agree with a recent writer in whose opinion the occurrence of a sharp febrile reaction has been rather useful than otherwise in very prostrate patients. The pyrexia, amounting to 103°F. „

" or even 104° F. in some cases which I have observed, cannot but have some detrimental effects upon the cardiac muscle. Similarly, the sudden oedemas are commonly accompanied by an alarming fall in blood tension. Two cases in my recollection, each suffering from only comparatively a mild attack of diphtheria, came to a fatal issue as the result of exhaustion following a severe attack of serum sickness. The condition of anaphylaxis, I have fortunately not encountered as yet. The conclusions referred to earlier undoubtedly include certain main factors involved in the causation of this conditions; but that other elements enter into etiology is also advisable. Clinical experience proves that one particular series or batch of serum (probably from a particular horse) will cause a higher percentage of undesirable sequelae than another series; and may there not be other factors inherent in, or peculiar to, the patient himself?

In a paper entitled, "Serum Sickness and Sudden Death following the Hypodermic Administration of Antitoxin" by Dr. Miller and Dr. Root of Detroit, published in the "Therapeutic Gazette" for February 1910, the writers discussed this point, and in their conclusion suggest the possibility of a relationship between serum sickness and sudden death and "status lymphaticus or some allied condition" or, in other words, that these,,

" particular antitoxin sequelae may bear some connection with a greater or less degree of a "hyperlymphatic" state, if I may coin such an expression.

Following up this idea, with particular regard to serum sickness, and with a view of counteracting any tendency to this hyperlymphatic or hyperthymic state, a number of cases of diphtheria were given thyroid gland substance in the form of thyroid gland tablets (Parke, Davis, & Co.) simultaneously with and for some days following the administration of antitoxin. The dosage employed was, roughly, as follows: up to five years $1\frac{1}{4}$ grains daily, for six doses (decreased in infants); from five to ten years, $2\frac{1}{2}$ grains daily, for six doses; from 10 to 15 years and upwards, five grains on alternate days, for four doses. In all a hundred cases were observed, 15 receiving thyroid and 50 receiving none, the latter acting as control cases. The antitoxin employed was, in all cases, taken from a serum series which was clinically known to produce a large incidence of rashes, etc. My results may be tabulated thus:-

	Cases receiving thyroid.	Cases not receiving thyroid.
Total number observed...	50	50.
No sequelae...	29	22.
Simple rash...	15	12.
Serum sickness	6	16.

" The figures of the first and second sections are not particularly striking, but the large number of cases in the non-thyroid column which suffered from serum sickness, and the small number in the thyroid column, at least suggest that the thyroid gland substance has some effect in modifying the condition.

The number of cases under observation, however, is not sufficiently large to admit of the drawing of anything in the shape of a definite conclusion; Nevertheless, the results may be of sufficient interest to stimulate further observations in this subject."

Auer and Lewis,⁶⁸ from results obtained from experiments upon animals, base a theory that the respiratory symptoms seen in the graver forms of anaphylaxis are due to ~~spasm~~ of the bronchioles resulting in carbon dioxide poisoning, and recommend Belladonna or Atropin for use in the condition. This idea is interesting, as according to one of the older theories, asthma is of a similar nature.

A further addition is that of Moschowitz⁶⁹ who has found a constant eosinophilia in "anaphylactic diseases".

Whatever may be the primal factor, the fons et origo of the condition, it is more than possible that the elucidation of the problem will bring with it the solving of many of the other riddles of medicine.

"Idiosyncrasy" whether shown in the shape of drug reactions of often untoward nature or in an attack of urticaria after the ingestion of an oyster; "susceptibility" to certain diseases; heredity "predisposition"; and even the fundamental question of "Immunity" itself, may all be stripped of their mystery.

The falling of an apple was the first step which led Newton towards the enunciation of the Laws of Gravity, and the present day uses of steam are but the result of the bursting of Watt's kettle. And it may be that Behring's Anti-Diphtheritic Serum, by the phenomena incidental to its use, will revolutionise all our preconceived ideas of medicine.

Serum Rashes: Serum Sickness, etc.

Serum rashes, or antitoxin eruptions, were as previously stated, early noted as sequelae to the injection of serum, antitoxin or other.

The laboratory side of the question has been discussed, and it is proposed now to confine the remarks to the purely clinical aspect.

Serum rashes are of two essential kinds, urticarial and erythematous. The latter may assume types uncommonly like the rashes seen in scarlatina or measles; or may display in their arrangement the circinate, annular, gyrate, macular and various other forms, all of

which may best be included in the term "multiform", Combinations of the various forms may not unusually be seen, but, speaking generally, the urticarial eruption is the commonest reaction, and moreover, is the one most usually seen in the simple case which one terms "serum rash". The erythemata are usually seen in the more severe reactions and I have found are uncommonly associated with fever of a continuous order; and with other symptoms about to be described.

Associated with these sequelae, there are a few aetiological factors which are worthy of consideration.

In the course of continuously observing cases of diphtheria under treatment, as in a Hospital, one is struck by the variations in incidence of rashes, etc. The personal factor, whilst influencing the reaction of this particular patient cannot also influence a series of cases. Investigation showed that the gross variations were coincident with the use of particular consignments of serum. It was found that Series A. produced a relatively much greater number of rashes than Series B.; whilst the patients receiving Series C. might display practically no sequelae. The obvious inference is that the horse from which Series A. serum was obtained was richer in the rash-producing element (or antigen) than those which gave Series B. and C.

Some have suggested that the mode of manufacture

may have some relation to this matter. We have given extensive trials to sera obtained from the larger manufacturers of England, America and Europe, but the same results have been observed in all. The serum of Messrs. X may show a most desirable lack of untoward phenomena for a few weeks, and then a fresh consignment will be started with, and most disturbing rashes etc. ensue.

Certain observations with one brand of serum were peculiar. This serum, made locally was sometimes sent to us within a very short period of being "bottled" so to speak. And it was noticed that frequently, though not as an inflexible rule, the fresh serum gave heavier rashes than serum matured by age. This may have been simple coincidence, but is nevertheless interesting.

Another fact observed is that those cases which display enlarged tonsils, adenoids, etc., show a greater tendency to "serum disease", i.e. the rash associated with rhinitis, adenitis, fever, etc. than to simple rash.

Rolleston has expressed the view that the serum rashes etc. are proportional to the amount of serum given in excess of that actually required, or in other words that the phenomena vary in their severity in direct proportion with the amount of serum given, and in indirect ratio to the severity of the attack. My experience will not permit me to agree with this sentiment. All cases admitted to the diphtheria wards here have a

serum injected at once although this or that may be an obvious quinsy; and the bacteriological examination is not waited for. Presuming that that the theory enunciated above is correct, then all the non-diphtheritic cases, i.e. tonsillitis, quinsy, etc. should have serum rash, etc. But such is very far from being the case in my experience; in fact, quite as large a proportion of the non-diphtheritic cases escape sequelae, as of the definitely diphtheritic.

Another clinical point noticed is that patients of a "rheumatic diathesis" react markedly i.e. in regard to rash, etc. after serum; and these patients generally show a profuse urticarial rash, and the pains in the joints when present are more amenable to antirheumatic treatment.

A further classification of rashes is possible. Sometimes the patient develops the rash at the usual time. This disappears and for some days the patient is quite well. Then the rash may reappear, and occasionally is more severe and accompanied by symptoms classed under "serum disease". We are in the habit of denoting these as "primary" and "secondary" rashes respectively.

On one occasion I have seen a third appearance.

John G. aet. 3. Had 32000 units in two injections of 16000 the second being 16 hours after the first. "Tracheotomy". Brisk urticarial rash at end

of second week lasting two days. Adenitis accompanying erythematous rash and rise of temperature in 4th week, lasting six days. Transient erythema with slight adenitis and fever in sixth and seventh week, of four days duration.

The primary rash etc. may be mild or severe. The secondary attack is more often severe than otherwise.

All the eruptions display a marked characteristic feature in their fleeting or evanescent nature.

A patient may be covered with urticarial wheals or erythematous blotches, and in an hour or so show only a few isolated patches; the lapse of another hour or two may find him in as pitiable a plight as the first. Even the scarlatinal types show this feature in a modified degree. The rash on the chest may be dull and angry after the type of the purplish rash of a toxic or septic scarlet fever, whilst that on the abdomen or back may by comparison appear much less severe. Local variation in intensity, the variation being manifest both as to time and place, is a very important point, in our view, in the differential diagnosis of serum rash from scarlet fever.

Itching, particularly marked in the urticarial rashes, is usually present, though it may vary in degree.

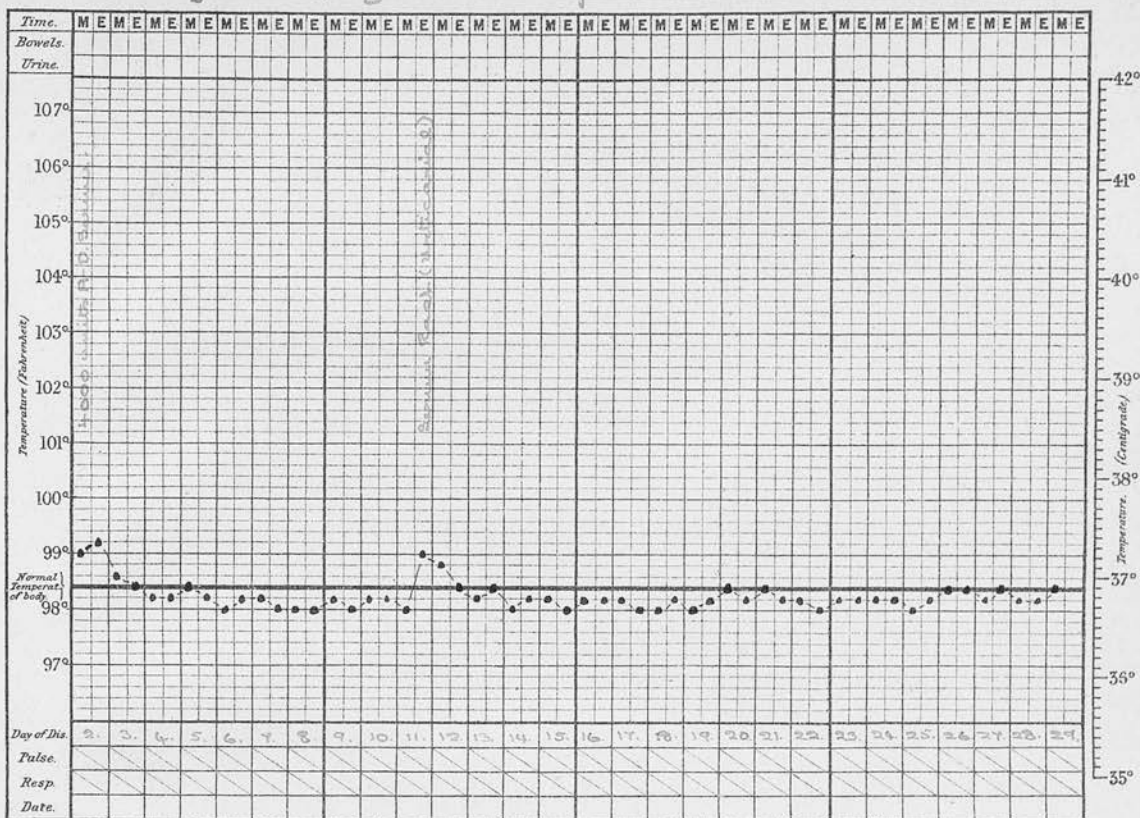
Symptoms and Course.

The commonest type is that of the appearance of an

urticarial rash of variable extent in distribution, as a rule in 10 to 12 days after injection. There may be prodromal symptoms for one or two days or a few hours, consisting of local redness or itching of skin near the site of inoculation; sometimes the skin near the site may show a degree of hypersensitiveness. Many observers mention tenderness of the local glands as being common in this form of rash. I have found such a condition rather rare than otherwise. Commencing at the site of injection the eruption may remain limited here, or it may spread quickly over the entire body. Associated with a rapid development of urticaria one has not infrequently seen a marked fall in blood pressure, resulting ⁱⁿ some cases, in an alarming collapse. The face is sometimes covered with rash, and a puffy bloated appearance is given. The eyes are congested, and there may be some lachrymation in this type. Children are by no means infrequently rendered somewhat croupy, the result of the rash involving the respiratory mucous membrane. Itching may be intolerable, with the result that the patient's body is covered with the marks of his nails.

Fever of a mild and transient degree may be present. Even when marked it usually is normal in a few hours. Chart I illustrates this effect in a mild case. The pulse is usually quickened. There is not

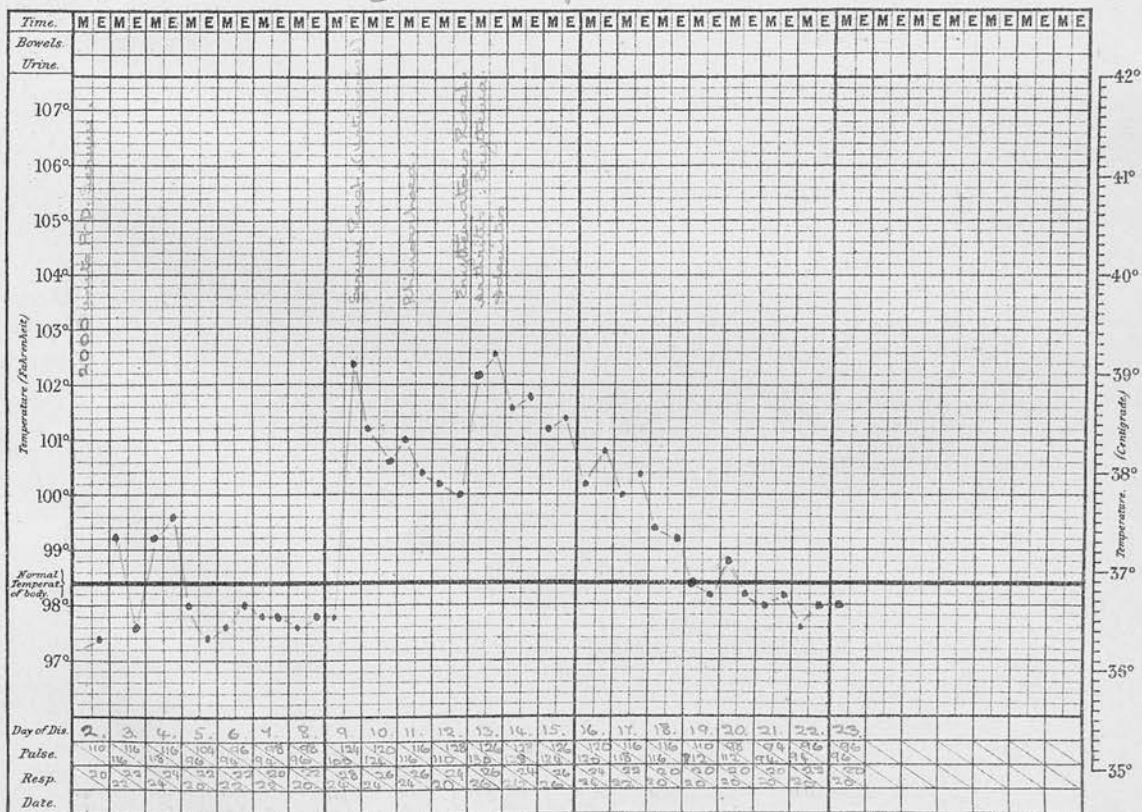
Name	Age	Disease	Result
Emily S.	4 yrs	Diphtheria	Recovery



Printed and Published by Widderspoon & Co. 8, Gate Street, Lincoln's Inn.

CHART T.

Name Walter B. Age 6 yrs. Disease Diphtheria Result Recovery



uncommonly pains in the joints and some swelling, most usually of the metacarpo-phalangeal joints, the wrists, the elbows and the knees. The pain is mainly on movement only. Adenitis, in my experience, is not a prominent symptom in this type. There may be slight malaise, and occasionally slight vomiting.

To the above cutaneous symptoms the term "serum rash" is applied. It corresponds to the "normal reaction" of Von Pirquet and Schick.

The duration varies from a few hours to one or two days.

Treatment is mainly symptomatic. An ointment composed of menthol and paraffin will ease the itching. Cold compresses sometimes soothe the painful joints; the salicylates do not as a rule cause any marked diminution in the pain, though I am inclined to think that Aspirin does to some extent give relief.

Sometimes however, the mild course thus outlined is not taken. The symptoms found may be much more severe and other symptoms of a general constitutional disturbance may be superadded. To this type the name "Serum Sickness" has been given. It is essentially the "Serum Rash" plus symptoms suggesting a condition in the nature of a variable degree of toxæmia and septicaemia.

The onset is generally abrupt. There is, not unusually, for a few hours before, general malaise. An

attack of vomiting commonly ushers the condition in. The temperature suddenly rises to 101° or 102° , and occasionally to 103° or 104° . The pulse is quickened though not to the disproportionate extent that is seen in scarlatina. The throat may be congested, or even inflamed and slimy, and the cervical glands are commonly inflamed, swollen and tender. Fairly frequently the soft palate shows a degree of mucous injection, disconcertingly similar to that of scarlatina. The tongue is generally coated, but after a few hours may be bright red with raised papillae, in fact a perfect "strawberry tongue". The conjunctivae are occasionally congested. The rash in these severe cases is usually of the Erythematous variety and commonly assumes the scarlatinal type. It may commence at the site of inoculation and remain limited there for a time. Not infrequently however, it soon spreads over the trunk and limbs and finally invades the face. The "circumoral pallor" described by some as pathognomic of scarlet fever, is occasionally seen beautifully portrayed in serum sickness.

One or two points in regard to the rash must be mentioned: The face is not infrequently usually attacked until late; and the rash is not infrequently rather heavier on the extensor surfaces.

Occasionally the temperature is much lower than

the dull angry purple rash would seem to justify - i.e. when considered from the "scarlatinal" point of view. The most important characteristic however, is the irregularity and evanescent nature of the local degrees of intensity. Frequent observation discovers that the rash is continually "in and out", heavy here at one time it seems to have faded considerably in a short time. Whilst there the rash, which was previously not angry looking, has become very pronounced. On the trunk this is particularly noticeable.

Occasionally one or more small urticarial patches are seen. It need only be merely mentioned that such a discovery is of vast diagnostic significance.

Or the rash may be of the morbilliform type of erythema. I have not seen so many of these cases, as like measles as some have described. The course of spread is usually the same as mentioned in the preceding paragraph. The rash is not usually raised or "velvety". One must admit however, that occasionally a case arises which gives real difficulty in diagnosis particularly, as not uncommonly happens, if the mucous membranes are involved in the exanthem and slight and slight coryza results. The suffusion of the eyes and the consequent "bleary" expression may also add to the morbillar clinical likeness.

On rarer occasions, the polyform, gyrate etc. types of rash are seen.

The patient commonly complains of pains in the joints, as described. In 24 hours or so from the onset, rhinorrhoea may commence, and on rare occasions I have seen in young children, slimy, mucous, frequent stools. Some children too show croupy cough, and at times a slight degree of dyspnoea. Otitis is comparatively not uncommon, and serum disease as far as my experience goes is commonly the cause of otorrhoea due to this otitis. Albuminuria is by no means rare.

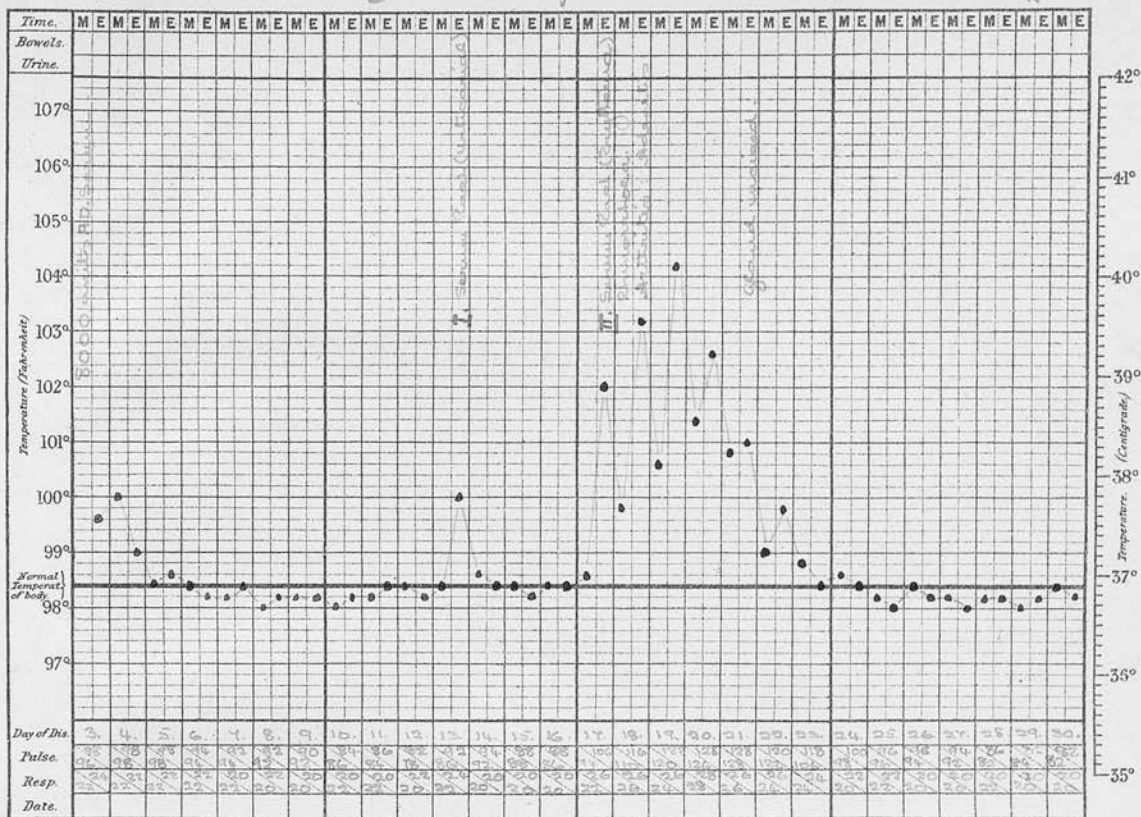
There may be oedema of the face.

I have on two occasions, seen polyuria with marked thirst as a very prominent symptom. Both cases were very severe, one ending fatally. The boy, who ultimately died, (Kenneth M., aet. 5) had thirst of such marked degree that on one occasion after having the bottle shaped urinal given to him, drank the contents which he himself had voided, in the momentary absence of the nurse. On another occasion the same boy, pleaded with his neighbour (a boy of 7 who related the incident to his nurse) to reach him his, when he had relieved himself.

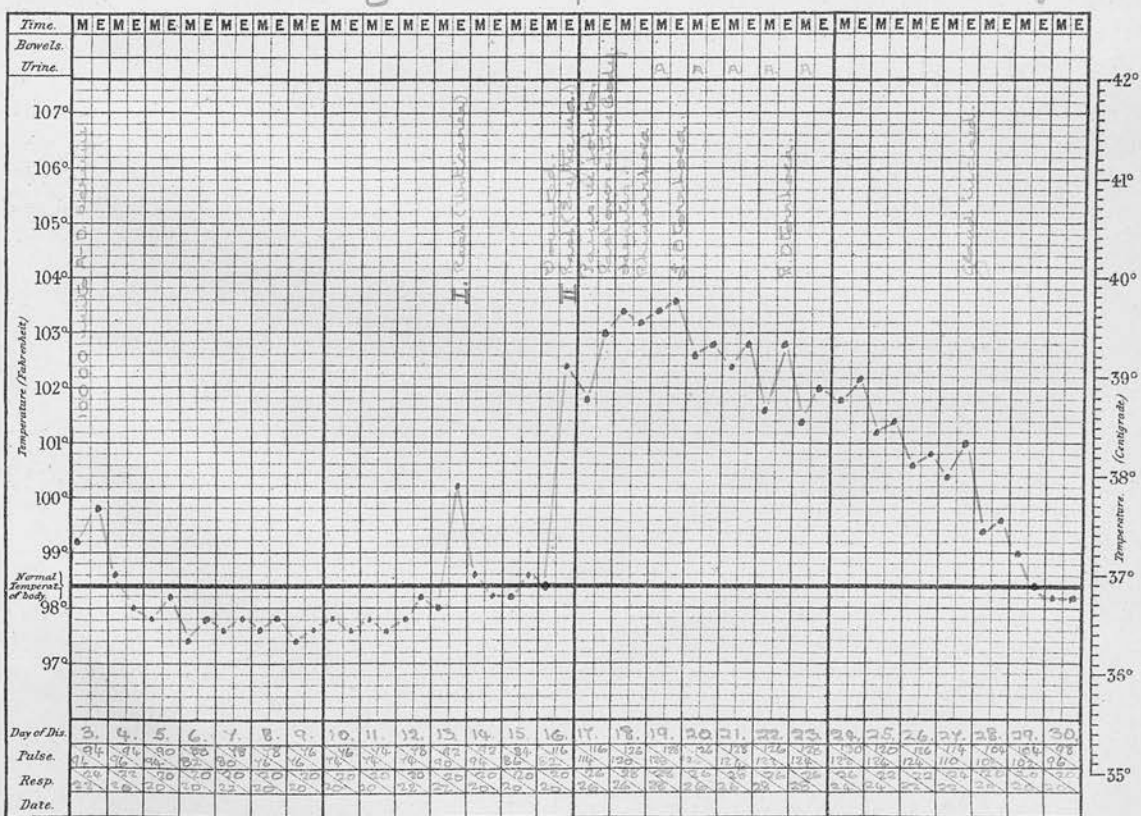
On one occasion (Effie T. aet. 7 Chart V.) in a marked case, I have seen kerato-iritis of a marked type occur. Septic changes in the glands not uncommonly take place and incision is demanded.

On three occasions each of the cases being compar-

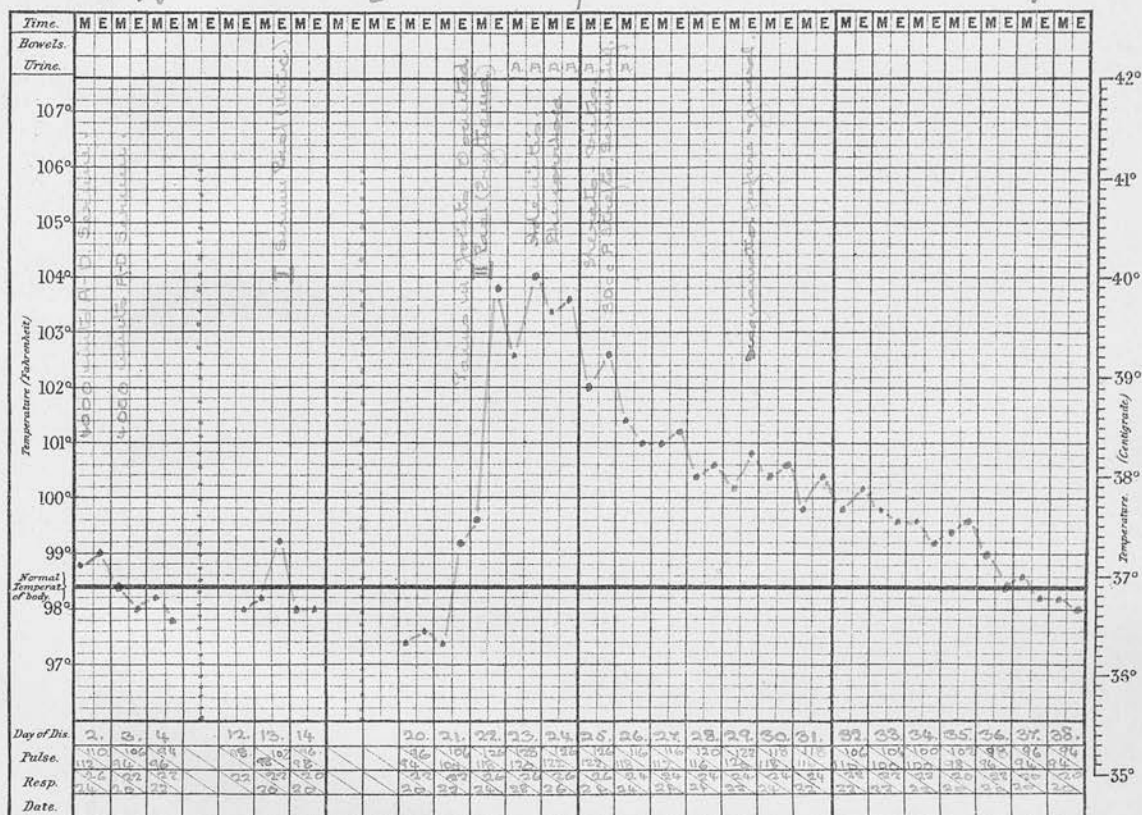
Name James H. Age 5 yrs Disease Diphtheria Result Recovery



Name Mona B. Age 5 yrs Disease Malaria Result Cure



Name Offie J. Age 4 yrs Disease Diphtheria Result Recovery



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CHART V.

actively mild as to diphtheritic infection, death has occurred, as a result of serum disease by reason of the low condition to which the patients were drawn. It occasionally happens, as previously stated that a secondary attack of serum rash takes place. The common course taken is that displayed on Charts III., IV., and V. The normal rash appears at about the usual time and the symptoms disappear within a day or two. Then after a period varying from two days to 4 or 5 weeks there is an abrupt onset of the symptoms constituting serum disease. The most usual time of occurrence is about seven to fourteen days after the primary rash. The exact nature of these secondary manifestations, I am quite unable to explain. Single injection or repeated dosage appears to bear no relationship; nor does severity of diphtheria seem to have any association. Whether or not it is due to a reformation of antibodies, one cannot say, but the symptoms certainly suggest a disturbance not unlike a toxæmia with some degree of septicaemia. Great difficulty is experienced when describing serum sickness in keeping to a "type". Each case varies a good deal from its fellows, one case showing a train of symptoms, more prominently than another.

Considered separately, the symptoms are:-

Incubation Period:

On an average appears to vary between 8 and 12 days. On rare occasions one has seen a very transient erythematous rash appear on the third day after injection. If of the scarlatinal type this rash is alarming, suggesting as it does the possibility of a true scarlatinal infection.

Fever:

Is sometimes present without the rash, and conversely is occasionally absent when the rash is present. In severe cases, after the sudden rise it remains high for 36 or 48 hours and then assumes a remittent falling gradually by lysis.

It is usually sudden in rise, very temporary, and sudden in fall, in the case of the urticarial rashes. The erythemata, particularly the scarlatinal rashes usually cause a maintained high temperature with a gradual return to normal. The temperature usually walks hand in hand with severity.

The Rashes:

1. Urticarial: Is the commonest of all types and is usually the simplest. It may be local only or it may be generalised. Itching is always marked and generally there is some local oedema, particularly of the face if the rash attacks that part. It invades the mucous membranes of the respiratory and intestinal tracts, and may result in symptoms of a croupy nature

or be the cause of intestinal irritation and diarrhoea.

Its sudden onset if extensive may cause some degree of collapse.

2. Erythematous. This type is commonly preceded by the urticarial: It sometimes occurs as a very early primary rash, though only rarely so; more generally it is as a severe rash with a normal incubation. In the severe types it may assume the annular form. The scarlatinal type is one of the most important from the diagnostic point of view. I feel convinced that many of the cases of so-called ^{cases of} "mixed infection" of diphtheria and scarlet fever are really diphtheria cases showing the scarlatiniform variety of erythematous serum rash.

The differential diagnosis is a matter of very real difficulty, and it is rendered even more complex by the ever present possibility of the occurrence of a case of true scarlet fever in a diphtheria ward.

The main points to notice are:-

The order of appearance of the exanthem, the site of inoculation, not infrequently being the first area affected. The face may be attacked ^{last} ~~fast~~: The local variability in degree of intensity and the "in and out" character of the rash: The extensor surfaces may show a relatively heavier rash: The presence of urticarial lesions, however limited, is obviously conclusive evi-

dence pro serum rash.

The pulse, though quickened, does not show that altogether disproportionate rapidity that is commonly noted in scarlatina.

Desquamation which almost always occurs, is heavy, generalised, i.e. pursues no definite order and commences earlier, and is completed sooner than in scarlatina.

The Moribilliform rash is not unusually associated with serum sickness, and at times may cause much perturbation in the mind of the physician, particularly if the patient is rendered "blotched" and "bleary" by much facial involvement. The absence of Koplick's spots on the buccal mucosa, the lack of the "velvety" nature of the rash; the possible absence of "prodromal temperature"; and the later appearance of the rash upon the face may all be points of significance.

Adenitis:

Is fairly common, though not the invariable symptom that some writers maintain it to be; when established it commonly helps to maintain the high temperature. The inflamed glands generally subside *pari passu* with the "disease".

Joint Pains.

Next to rashes and fever are the commonest symptoms. There is usually some swelling, which, in my opinion,

may be part of the general oedema of the mucous (or serous) surfaces. The condition superficially resembles that of acute rheumatism. Salicylates however, do not markedly control it nor is endocarditis or pericarditis associated with it.

Aspirin (Aceto-salicylic acid) would appear to give more relief than the pure salicylates.

Albuminuria.

Is met with fairly frequently in those cases showing a continuously high temperature, and is therefore presumably due to the febrile state.

Treatment of Serum Sequelae.

As previously stated, the treatment is mainly symptomatic when the condition is established.

Various prophylactic measures have been recommended with a view to diminishing the liability to its occurrence.

Calcium chloride, given for some days after the injection of serum has been widely recommended. Its use has not been attended with marked success however; I have tried it and also the Lactophosphate of Calcium but have not noticed any beneficial results.

Thyroid gland has already received mention in the section dealing with Anaphylaxis. The use of concentrated sera, antitoxin-globulins, "dry" sera, etc. has been mentioned previously as being advantageous in this respect.

V. Results and analysis of Cases.

This section comprises a brief survey of the entire series.

In dealing with the deaths within 48 hours of admission to Hospital, and the figures relating to Laryngeal cases and Tracheotomies an explanation is necessary.

The City Hospital East, is situated near some of the more densely populated portions of Liverpool and the greater share of the available accommodation for diphtheria for the City is allocated therein. Consequently the majority of the "urgent" cases reported are promptly brought in this Hospital by Motor Ambulance, with the result that our statistics in this particular regard are disproportionately high.

Total number of cases under review = 1596.

These 1596 cases were composed of 812 females and 784 males.

The total number of deaths = 185 or 11.59% in which again the females were slightly in excess of the males.

74 or 40% of these deaths took place within 48 hours of the patient's arrival at the Hospital. Various factors are to be considered in seeking the cause of this delay in removal. Ignorance, callousness or prejudice "against Hospitals" on the part of parents

are potent in this respect.

The cases and deaths analysed in regard to age periods, are shown on Table C. The greater fatality of the disease in young children is very evident.

Table A. in a previous Section also is of interest in this regard.

The youngest patient in the series was 12 weeks old and the oldest was 70 years.

	Under 5	5-10	10-20	20-30	30-40	40 & up.	Total.
No. of cases.	577	544	330	110	24	11	1596
No. of deaths.	129	51	5	-	-	-	185
% age mortality.	22.35	9.55	1.21	-	-	-	11.59.

Table (C) showing Mortality for different age periods.

The "Causes of Death" in the series "Diphtheria" of course constituting the "primary" one, were:-

Cardiac Paralysis (per se).....72.

Cardiac Paralysis (Secondary to other Paralyses)..16.

Toxaemia.....53.

Broncho-Pneumonia.....23.

Lobar Pneumonia.....5.

Septic Pneumonia.....2.

Empyema.....2.

Serum Disease {Syncope 2.
Septic Meningitis 1.}.....3.

Haemorrhage (post operative).....	1.
Syncope (during Tracheotomy).....	4.
Diphtheria and Scarlatina (Uraemia).....	2.
Diphtheria and Tubercular Meningitis.....	1.
Diphtheria and Tabes Mesenterica.....	<u>1.</u>
	<u>185.</u>

The 1596 cases represent the results from 2053 notifications of cases as "diphtheria" or its usual synonyms.

The 457 cases thus wrongly diagnosed included:-

Commonly:-

Tonsillitis, Scarlet Fever (generally of the "septic" variety), Measles, Broncho-pneumonia, Laryngitis, and Syphilis.

Less commonly were:-

Stomatitis, Tuberculosis of Larynx (2) Enteric Fever, Bronchitis, Cellulitis, Retro-pharyngeal abscess, Laryngismus Stridulus, etc.

Of these 1596 cases,

1491 were both clinically and bacteriologically confirmed as Diphtheria.

The remaining 105, or 6.5% did not give a "positive" bacteriological result, but were clinically typical cases.

Of these 1596 cases,

249 (15.5%) showed laryngeal symptoms, and trach-

eotomy was necessitated in 152 (9.5%) cases.

Out of these 152 cases of Tracheotomy,

53 died, i.e. 34%.

42 of these fatal cases were under 5 years of age.

9 were between 5 and 10 years, 1 was 13 years and 1 was 16 years.

(This last case, in a fit of coughing, 10 hours after removal of the tube ruptured a vein exposed by the original incision and, inspiring a quantity of blood, was literally "drowned".)

The most fatal years were the first two years of life. No case under 1 year tracheotomised for diphtheria, in the series, recovered.

One case, a boy aet. 6, had tracheotomy performed twice, the second 12 months after the first. He made a good recovery.

Table A (page 39) shows the mortality arranged in relation to age, and day of disease on admission.

Table B (page 40a) shows the effect upon mortality of the day of disease when serum treatment was commenced.

Concurrent Infectious Diseases.

9 cases showed chickenpox.

4 cases showed mumps.

4 cases developed erysipelas.

3 cases showed whooping cough.

3 cases showed measles (in acute stage).

2 cases showed scarlet fever (in acute stage).

Serum rash etc. occurred in 697 cases, i.e. in 49.3% of the recoveries, or 43.6% of the total cases.

Of these 697 cases, the original rashes were:-
Urticarial, 373, and Erythematous, 324.

Secondary rashes were observed in 192 cases, and of these 116 were erythematous, principally scarlatini-form, and Morbilliform, the remainder being multiform or urticarial or mixed.

Paralysis, including cardiac paralysis, occurred, in one form or another, in 337 cases or 21.1% of the total number.

Total cardiac paralysis (primary or secondary to paralysis elsewhere) accounted for 88 deaths, or 47.5% of the total deaths.

Expressed otherwise, the death rate in the series of 1596, from cardiac paralysis (primary and secondary) amounted to 5.5%.

The remaining paralyses, involving 249 cases (15.6%) in the series, were principally of the palate, the extrinsic muscles of the eye, the lower limbs, and multiple type.

Two cases of intestinal paralysis occurred in the series.

No case of facial or diaphragmatic paralysis was

observed.

Herpes on the lip was noted on 49 occasions.

SUMMARY AND CONCLUSIONS.

Diphtheria is an infectious and contagious disease characterised by a local lesion resultant upon the invasion and proliferation of the Klebs Loeffler Bacillus, and a constitutional manifestation of symptoms and sequelae, due to the absorption of the toxins elaborated by the specific bacillus.

The specific antitoxin serum is both curative and prophylactic. It does not cause post-diphtheritic paralysis, the increase in incidence being only an apparent one, the result of better diagnosis and classification, and of life being preserved in a larger number of patients.

The earlier the stage of the disease in which the antitoxin is administered, the greater are the chances of successful treatment, as the beneficial effects of the serum progressively and increasingly depreciate with each day that passes without its administration.

It is a false economy to give antitoxin in other than a liberal dosage.

Certain grave phenomena are seen as sequelae to the injection of antitoxin and other sera. These occurrences, it would appear, are commonly associated with persons of the asthmatic or "angio-neurotic" diathesis. Therefore, rare as are these anaphylactic conditions, it nevertheless behoves the exercise of careful consid-

eration, before submitting such persons to subcutaneous administration of serum of any kind.

Anti-diphtheritic serum may be given per os or per rectum with beneficial results.

For prophylactic purposes antitoxin given by mouth is quite efficiently protective.

A livelier appreciation of the nature and dangers of diphtheria on the part of the public at large would result in a marked decrease in the mortality of the disease, by reason of the children being sent to Hospital, or otherwise receiving appropriate treatment at an earlier stage of the disease.

"Diphtheria carriers" and undiscovered diphtheritic infections of the nose and skin particularly, may be potent factors in the spread of the disease, especially in the case of schools and other institutions in which young persons are congregated.

The supplying of antitoxin by Local Sanitary Authorities to Medical Men gratis, should be an invariable rule throughout the country.

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APPENDIX.

Showing suggested lines of a leaflet which might be issued by Local Sanitary Authorities to Medical Men in the district.

A few guiding signs in the treatment of diphtheria:-

1. Do not wait for the result of bacteriological examination, save only in the mildest of cases, but inject at once. Time lost severely handicaps the chances of the patient; and 2000 units on the first day are of more value to the patient than 6000 on the 3rd or 4th.
2. Laryngeal cases require a very large initial dose, at least 10000 units being injected. Repeat the dose in 10-12 hours if signs of relief are not evident, and again if necessary.
3. Similarly, nasal case of the acute type require much serum, also do those cases where the membrane involves the tonsils and nose of larynx.
4. Notify the Authorities as early as possible, and when speedy removal to Hospital is required, please state to that effect.
6. If a case of Diphtheria occurs in a house, take a "swab" of the throat of each of the other occupants, and give such a dose of antitoxin as a prophylactic

Table showing roughly the amount of antitoxin required, taking into consideration the site and extent of lesions and the day of disease.

A	B	C	D	E	F	G	H.
Day of disease	Tonsils only	Tonsils & fauces.	C. plus uvula & soft palate	Nose.	Larynx & below	E plus B or C.	F plus B or C.
1.	1000	2000	3000 *	6000	10000	3000 *	10000 *
2.	2000	4000	6000	8000	12000	10000	14000.
3.	4000	6000	3000	8000	14000	12000	16000.
4.4.	4000	8000	10000	10000	16000	14000	16000.
5 & up.	6000	8000	10000	12000	16000	16000	20000.

*Conditions as severe as these are unlikely to be reached in so short a time as the first day of illness.

measure; about 10000 units is enough to give hypodermically, or 2000 units may be given per os "on an empty stomach", with a little normal salt solution.

7. If a series of cases occur in a school be suspicious of a diphtheria "carrier", or of diphtheritic rhinitis or dermatitis. Bacteriologically examine all the persons in the building.
8. Antitoxin may be obtained gratis on application at the Public Health Office or the Isolation Hospital.
9. The table appended gives an approximate idea of the amount of serum to inject in the various types of cases,
10. Repeated injections are frequently necessary before real benefit is apparent. This is particularly the case in the laryngeal and acute nasal type of the disease.